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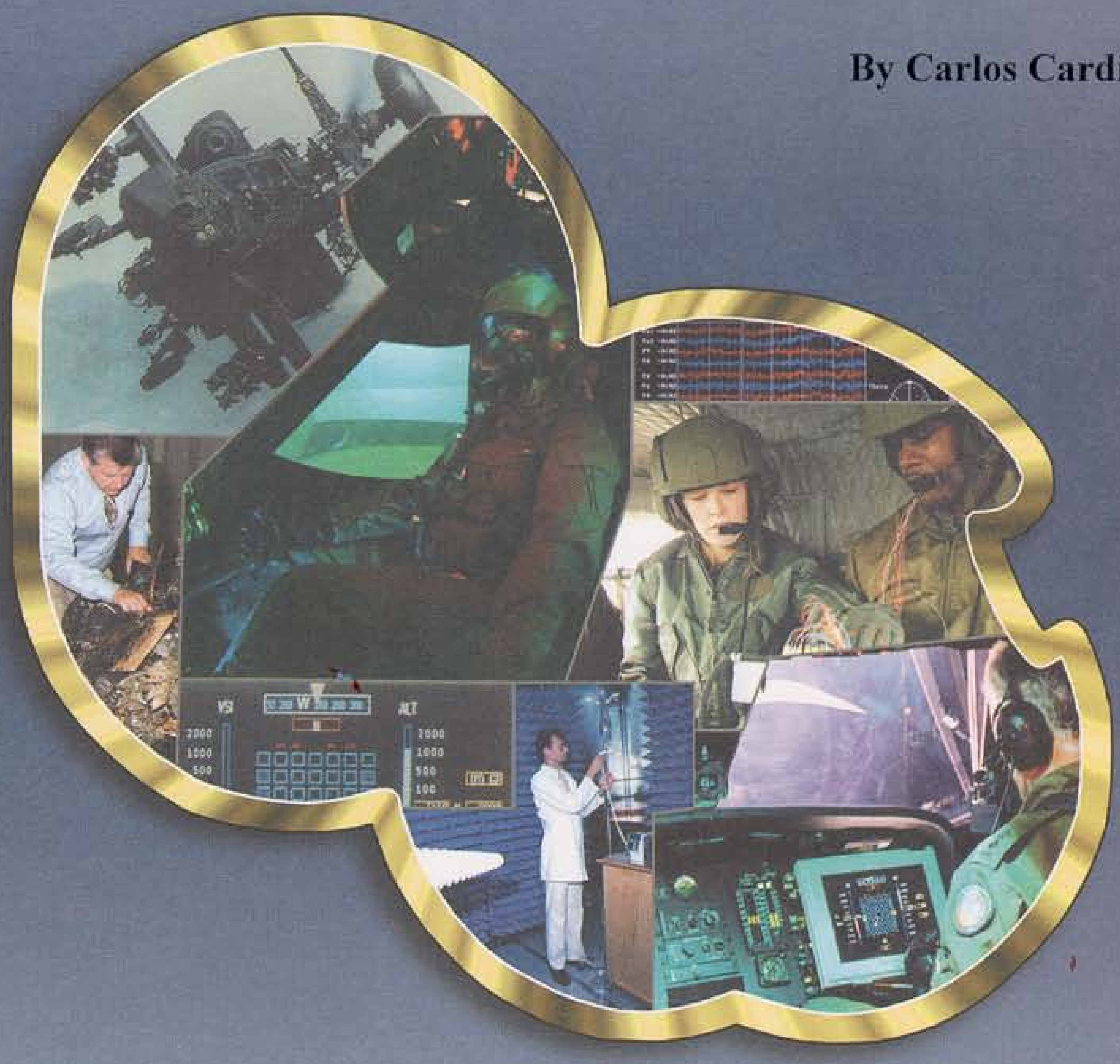
Quantitative Electroencephalographic (QEEG) Data Analysis for the Performance Sustainment of Two Man Crews Throughout 87 Hours of Extended Wakefulness with Stimulants (Dextroamphetamine, Caffeine, Modafinil) and Napping

By Carlos Cardillo



Sensory Research Division

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14. ABSTRACT
Military operations require army aviation units to operate around the clock during time of conflict. Sleep management, naps, and pharmacological fatigue countermeasures may be combined to assist in achieving successful military outcomes. We used QEEG methodologies in an effort to elucidate the CNS effects of stimulants (modafinil, dextroamphetamine and caffeine) and nap combined with the sleep deprivation factor. In regards to sleep deprivation effects, results indicate that by the end of the study all groups experienced increases in slow-waves (mainly delta) and decreases in alpha waves. Caffeine, modafinil, and dextroamphetamine, respectively, reversed during the initial 42 hours the electrophysiologic effects of sleep deprivation with smaller increases in delta activity and less deterioration of alpha activities. Caffeine and modafinil appeared to have the greatest degree of effect with respect to producing delays on alpha activity deterioration. (Continued on next page.)

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Alpha activity remained close to baseline levels for the first 46 hours. We observe a marked deterioration of alpha after 22 hours in the dextroamphetamine and placebo groups. There is virtually no increase in theta activity across the sleep deprivation cycle, for all groups, including placebo. These may represent effort levels consistently across all groups. Additional analysis could systematically correlate cognitive tasks and QEEG data for each pharmacologic intervention.

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Introduction

Military operations require Army aviation units to operate around the clock during time of conflict. The success of military operations, particularly in special operations units, depends on maintaining the speed and momentum of continuous day-night operations (Department of the Army, 1997).

To achieve optimal cognition, sustain judgment and decision-making, and enhance performance, we need to understand how to best manage personnel and missions involving acute total sleep deprivation, partial chronic sleep deprivation, and demanding cognitive workloads. To this end, sleep management, naps, and pharmacological fatigue countermeasures may be combined to assist in achieving successful military outcomes.

Amphetamine-like stimulants and caffeine are known to increase wakefulness, and their effects on the brain are well reported. Modafinil, unlike amphetamines, ameliorates sleep deprivation effects without generally stimulating the central nervous system (CNS). The pharmacological mechanism of modafinil is not completely known and is still under investigation.

The most direct indicator of CNS functionality is the electroencephalogram (EEG). The validity and reliability of quantitative electroencephalography (QEEG) methodologies in the classification of psychotropics were demonstrated based on retrospective and prospective studies (Herrmann et al., 1979; Itil et al., 1979). Itil (1981) discovered psychotropic properties of new drugs that could not be predicted by animal pharmacology and biochemistry. Additionally, EEG signals are clearly influenced by sleep deprivation (Lorenzo, et al. 1995; Pigeau, Heselgrave, and Angus, 1987).

In the context of such research, a large number of studies have employed different approaches in efforts to detect and classify patterns of EEG changes associated with pharmacological interventions and total sleep deprivation. In the present study, QEEG methodologies were used in an effort to elucidate the CNS effects of the study drugs combined with the sleep deprivation factor. Ultimately, determination whether the drugs were modulating brain activities in a predictable manner consistent with their performance effects will be sought. For example, if a pilot did not perform well, is that reflected in and can that be predicted by the QEEG?

In an effort to determine the electrophysiological effects and to help reveal the performance enhancing modes of action of the study drugs (caffeine 200 mg, dextroamphetamine 5 mg, and modafinil 100 mg) on sleep deprived pilots, the neurophysiological hypotheses are stated as follows: a) sleep deprivation of up to 68 hr (hr) will fragment awake EEG patterns, producing an increase on slow wave activities (1.3 to 7.5 cps) and a decrease on alpha and faster activities (7.5 to 14 cps); b) caffeine, dextroamphetamine, and modafinil will generate predictable and significant improvements on the EEG patterns when compared to placebo; and c) a 2-hr nap will attenuate the deterioration of EEG patterns produced by 68 hr of continuous wakefulness.

Methods

EEG recording and processing

EEG was continuously recorded from scalp electrodes in a standard unipolar setting (F7-A1, F8-A2, C3-A1, C4-A2, FZ-A1, CZ-A2, O1-A1, and O2-A2). The EEG isolated amplifier low filter was set at 1.3Hz, and the high filter was set at 70Hz. To accomplish the analog to digital conversion of the EEG signal, a 12 bit, 16 channels A-D board was used. The A-D conversion time is 10 microseconds, A-D throughput 27,500 samples/second, and the A-D channel acquisition time is 15 microseconds, with a system accuracy of +.05% full-scale range.

All EEG channels were processed and quantified using frequency analysis, where up to 20 frequency bands on each of the collected channels can be analyzed on-line using time-domain analysis (Itil, et al., 1987). This way, any range of bands can be specified for display or used for analysis. The resulting variables are average amplitude, amplitude variability (Drohoki), average frequency, and frequency deviation, along with twenty frequency bands (1.3 to 2.5, 2.5 to 3.5, 3.5 to 4.5, 4.5 to 5.5, 5.5 to 6.5, 6.5 to 7.5, 7.5 to 8.5, 8.5 to 9.5, 9.5 to 10.5, 10.5 to 11.5, 11.5 to 12.5, 12.5 to 13.5, 13.5 to 15.0, 15.0 to 17.0, 17.0 to 20.0, 20.0 to 26.0, 26.0 to 32.0, 32.0 to 38.0, 38.0 to 48.0, 48.0 Hz and up.). The selected epoch size for all channels was 5 seconds.

A specialized zero-cross analysis was used on the O2 lead only for Quantitative Pharmaco EEG analysis (Shapiro et al., 1977). This analysis analyzes not only the signal that crosses the baseline (primary wave) but also analyzes the superimposed EEG activity on the primary wave that does not cross the baseline (first derivative). The bands used by this analysis are set since the results are processed and compared against a database. This analysis reduces the QEEG to 22 variables, which are average absolute amplitude, amplitude variability, average frequency, frequency deviation, eight frequency bands for the primary wave (1.3 to 3.5, 3.5 to 7.5, 7.5 to 13.0, 13.0 to 20.0, 20.0 to 26.6, 26.6 to 40.0, 40.0 to 90.0, 90.0 Hz and up), as well as average frequency, frequency deviation, and eight frequency bands for the first derivative (1.3 to 10.0, 10.0 to 16.0, 16.0 to 20.0, 20.0 to 26.6, 26.6 to 40.0, 40.0 to 50.0, 50.0 to 90.0, 90.0 Hz and up).

Automatic online artifact detection was used during EEG recording, followed by an off-line visual inspection of the EEG to further select artifact free portions of the record for analysis and recalculate the means and standard deviations of the QEEG variables.

Procedures

In order to obtain an average of 20 artifact free samples for each recording, QEEGs were performed for 10 minutes, awake and with eyes closed. Each period was divided into two sub-periods, with an approximate 1 to 2 minute break between them. During the first five minutes, a standard eyes closed, resting EEG was performed, and no attempt was made to control the subject's vigilance level (the resting recording period is labeled RR). During the second sub-period, a random acoustic stimulus was presented at 7 to 45 second intervals and subjects were asked to respond to the stimulus by raising their thumb (the simple reaction time task is labeled

RT). The RT task was not actually intended to measure the subject's performance but rather to keep the vigilance at a relative constant level (control of spontaneous drowsiness).

Thirty-two subjects were scheduled for a full week at the U.S. Army Aeromedical Research Laboratory in groups of two and under the same drug condition. Due to technical mishap, data from two pairs of subjects (two subjects on placebo and two subjects on caffeine) could not be included in the analysis. Thus, data presented represents six subjects on caffeine, eight on dextroamphetamine, eight on modafinil, and six on placebo.

Among several other tests for the study, participants completed three QEEG training sessions on the first three days to adapt to the procedure and also to compare their QEEGs to a normative database to ensure that there were no significant deviations from normative patterns. Subsequent testing took place on 13 additional QEEG sessions (figure 1).

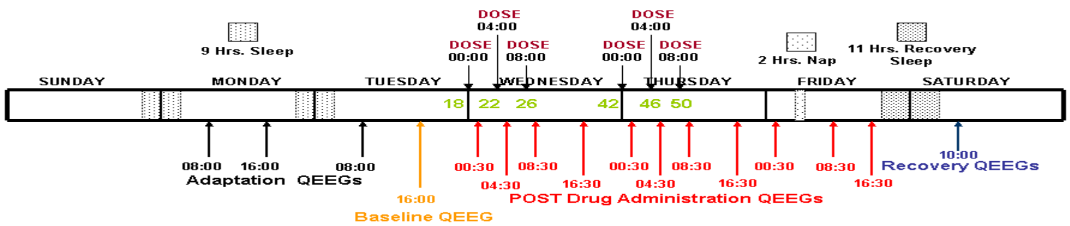

Figure 1. Timeline for drug and QEEG administration. The numbers in the center of the bar indicate the number of hr of continuous wakefulness at the dose time. On average, QEEGs were recorded between 30 to 40 minutes after drug administration.

Multi-lead evaluation

In order to determine the effects on multiple areas of the brain, a dynamic brain map system was used. With dynamic brain mapping, it is possible to view delta, theta, alpha, and beta activities of a multichannel QEEG recording in the form of a brain map. This way, the amounts of activities are displayed by color coding on an anatomically correct brain image. The QEEG data are displayed on the brain image in the exact location where the recording electrodes were placed, and the areas between electrode locations are interpolated using blending algorithms, thus depicting the total spread of the brain's electrical activity. The means of delta (1.3 to 3.5 Hz), theta (3.5 to 7.5 Hz), alpha (7.5 to 13.0 Hz), and beta (13.0 Hz and up) activity, over all subjects, for each session and for each drug group are averaged. Figure 2 depicts these maps for the rested (baseline) QEEGs for each group.

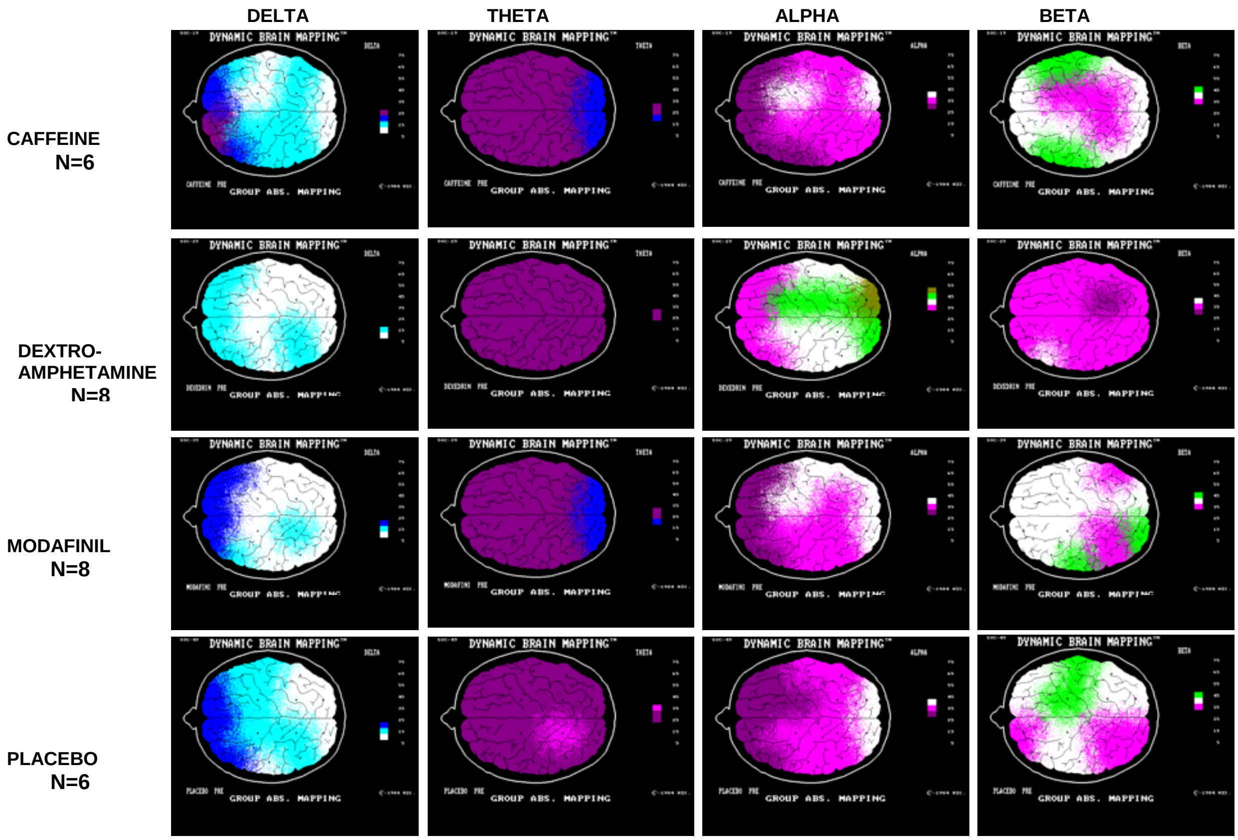

Figure 2. Rested EEG patterns. Four frequency bands for each drug group are represented as a brain map. As expected for baseline QEEGs, each frequency band showed similar patterns. The dextroamphetamine group showed a slight reverse pattern between alpha and beta activities when compared to caffeine, modafinil, and placebo groups.

To measure the difference before and after the drug, the baseline (pre-drug) was subtracted from each post-drug brain map to obtain a change from baseline state. Accordingly, any changes in brain map can be attributed to the effect of the drug, the sleep deprivation, or both combined. In this way, the effects of caffeine, dextroamphetamine, modafinil, and placebo could be analyzed as independent factors.

In order to determine the electrophysiological modes of action of the drugs and their regional topographic distribution, the QEEG activity of the eight recorded brain areas and thousands of mathematically interpolated brain areas were quantified. The percentage of delta, theta, alpha, and beta bandwidths in the recorded time periods were calculated before and after the beginning of drug administrations, and the changes in each of the time periods (18, 22, 26, 34, 42, 46, 50, and 58 hr awake) were compared with baselines values.

Results

Changes from baseline on the dynamic brain map for the four drug groups tended to show a systematic increase of delta activity and a decrease of alpha activity in all time periods, as summarized in appendix A.

Caffeine, modafinil, and dextroamphetamine, in that order, showed smaller increases in delta activity over all areas of the brain up until 42 hr of sleep deprivation (after three doses). Although alpha activity had the tendency to decrease as the number of hr awake increased, modafinil and caffeine groups showed virtually no changes from baseline until 46 hr of sleep deprivation, suggesting a delay in the deterioration or decrease of alpha activity. Dextroamphetamine and placebo, however, produced a systematic decrease of alpha activity right after the second dose (22 hr awake), with the highest increases shown on dextroamphetamine rather than placebo.

A systematic but slight increase of theta after the fourth session is seen in all drug groups, with the least increase in the caffeine group. However, no marked changes for any of the drug groups were seen in the theta activity levels.

Similarly, beta activity showed a systematic but slight increase in all sessions and in all drug groups, with modafinil having the least changes from baseline. The placebo group had a decline in beta activity after 46 hr, which produced a marked decrease of the activity after 50 and 58 hr of sleep deprivation.

Analysis of changes in QEEG variables based on O2 lead

Using the 22 period analysis measurements, QEEG changes from baseline to each session were calculated for each individual subject in terms of t-values for both resting recording (RR) and reaction time (RT). The individual profiles of the t-values are shown in appendix B. Visual inspection of the individual profiles showed, even though subjects on a particular drug group received the same treatment, their individual QEEG profiles differ considerably in both primary wave and first derivative.

Subsequently, drug-induced changes for each drug group were evaluated using t-statistics. The QEEG group profiles in each session for the primary wave and first derivative are shown in figures 3, 4, 5, and 6, where the 22 QEEG variables are plotted separated by RR and RT. Both the individual and the group profiles provided preliminary information related to the drug-induced changes on each particular variable before being compared to a database of psychotropic drugs.

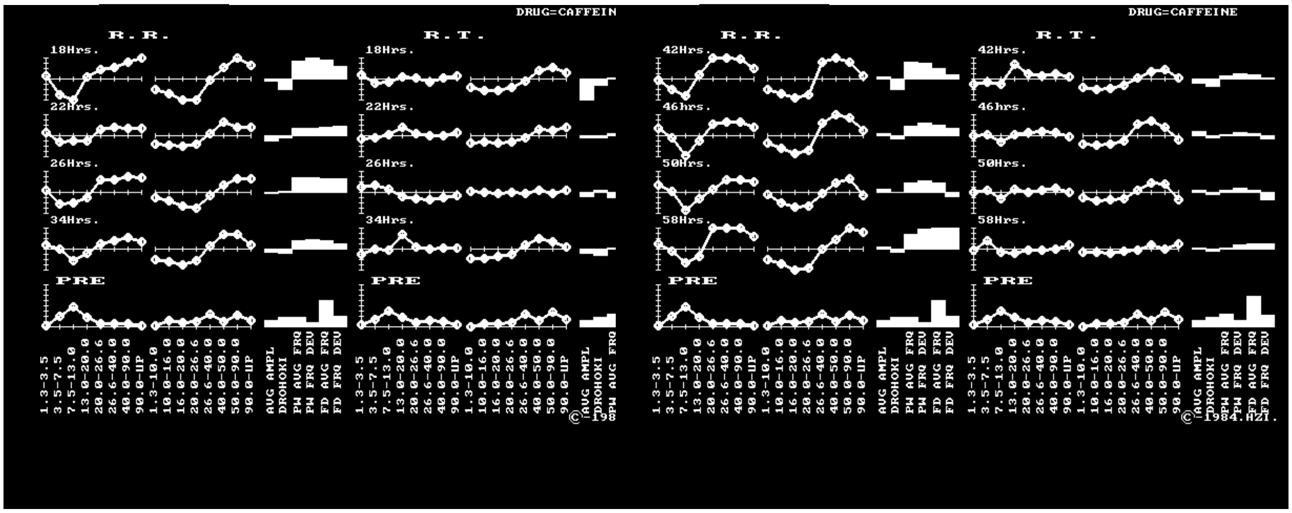

Figure 3. Caffeine group changes for the primary wave and first derivative. During the first 34 hr of sleep deprivation, the caffeine group showed primary wave decreases of lower frequencies (1.3 to 20.0 cps) for RR and virtually no changes on RT. From 46 to 58 hr, RR increased on the lowest (1.3 to 7.5 cps) and the highest (13.0 to 90+ cps) frequencies and no changes on RT. The first derivative showed constant decreases on lower (1.3 to 26.6 cps) and increases on highest (26.6 to 90+ cps) frequencies.

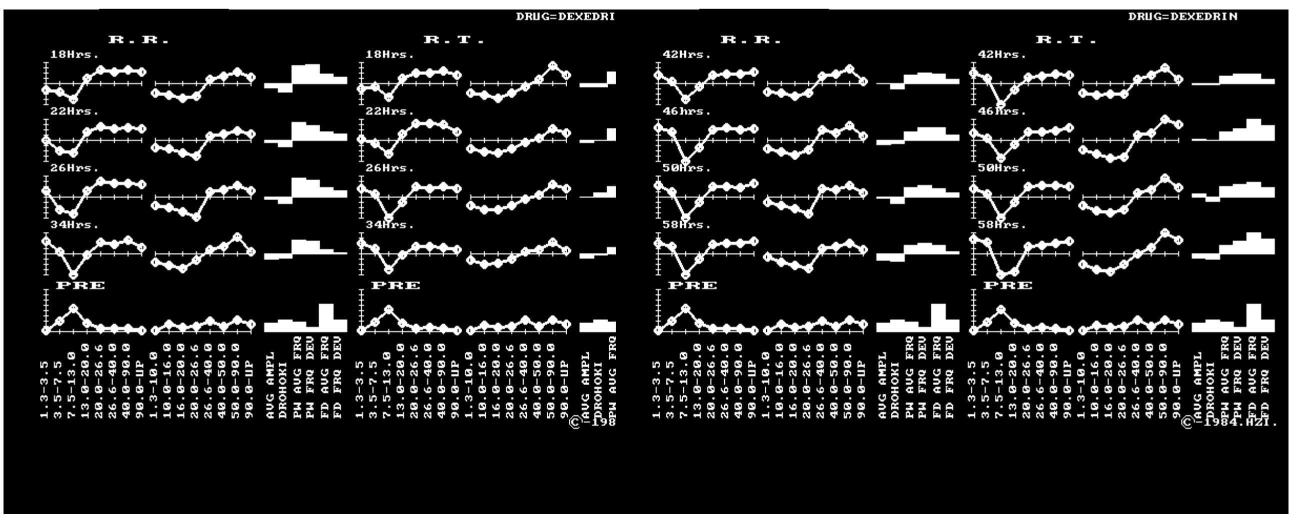

Figure 4. Dextroamphetamine group changes for the primary wave and the first derivative. Throughout all sessions, the dextroamphetamine group showed a decrease on the 7.5 to 13.0 cps bands for both RR and RT. After 34 hr, 1.3 to 7.5 cps bands showed constant increases. The first derivative decreased 1.3 to 26.6 cps and increased 26.6 to 90+ cps bands in all sessions.

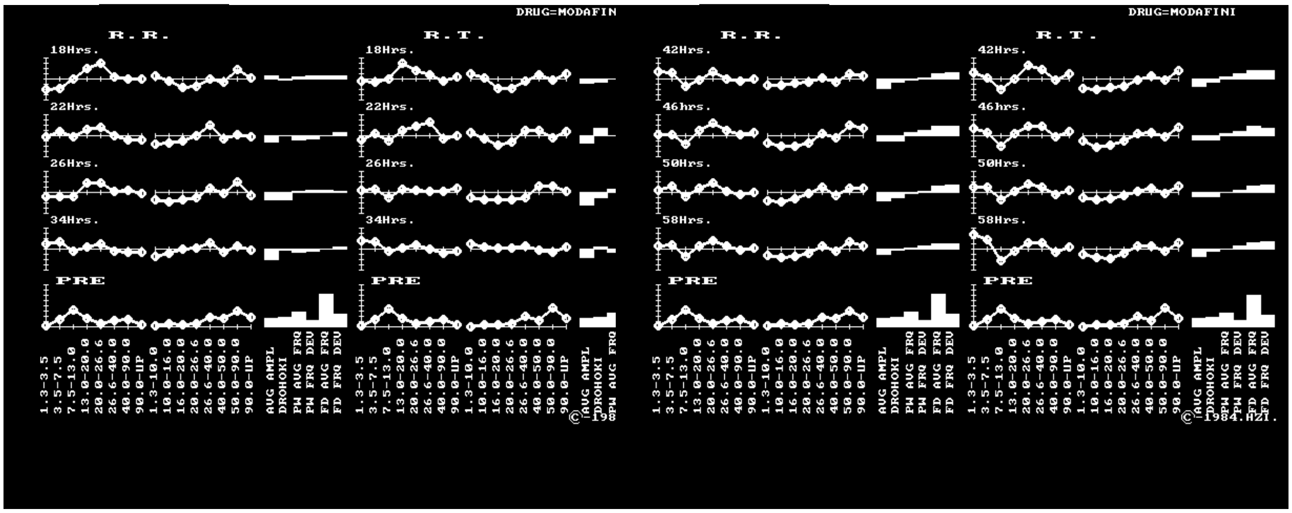

Figure 5. Modafinil group changes for the primary wave and the first derivative. The modafinil group showed virtually no changes on lower frequencies of the primary wave (1.3 to 26.6 cps) up to 34 hr of sleep deprivation. From 42 to 58 hr, there were slight increases of 1.3 to 7.5 cps and 13.0 to 26.6 cps and decreases on 7.5 to 13.0 cps. The first derivative decreased on 1.3 to 26.6 cps and showed no changes on 26.6 to 90+ cps.

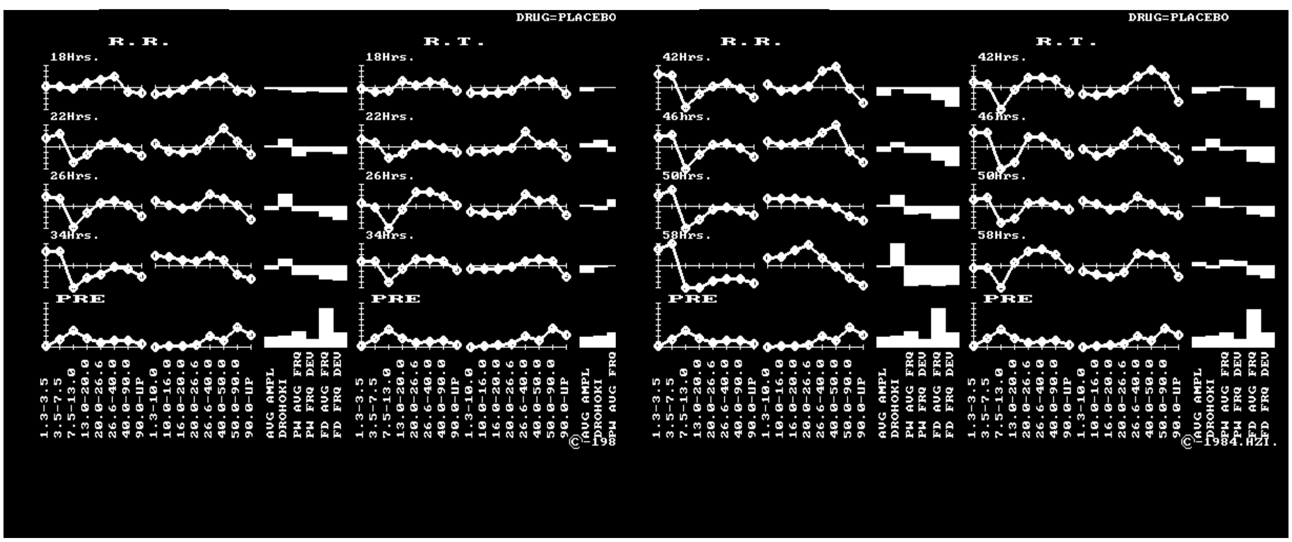

Figure 6. Placebo group changes for the primary wave and the first derivative. The placebo group produced increases of 1.3 to 7.5 cps mainly for RR and decreases of 7.5 to 13.0 cps for both RR and RT. The first derivative showed an increase in 26.6 to 50.0 cps.

Correlation with a database of psychotropic drugs

In order to classify the study drugs (mode of action), the QEEG changes induced by drugs in terms of t-values (QEEG profiles) of the period analysis data at O2 are compared with a database of psychotropic drug therapeutic groups (CNS depressants, anxiety relievers, mood elevators, and psychostimulants). The database is part of a QEEG-based classification system, which includes the QEEG effects, after one hour (1HR Database) and after three hours (3HR Database), of 85 well-known psychotropic drugs, established in 715 healthy volunteers and based on 79 quantitative pharmaco-EEG studies (Itil et al., 1974; Shapiro et al., 1975; Itil et al., 1979). The QEEG drug classification system is used based on both correlation and discriminant function analysis. Briefly, the basic input to the discriminant function model was the 22 component t-value vector at each of the conditions for the QEEG recording (18, 22, 26, 34, 42, 46, 50, and 58 hours for RR and RT). These data were input to stepwise discriminant analysis programs. The statistic used to classify the drugs was the Pearson product moment correlation, which provides a similarity coefficient. The shape of a drug profile in the database indicated that 22 QEEG measurements (not all independent) showed some changes from baseline to post-drug levels for a particular therapeutic group in terms of t-values. The t-profiles of the drug groups in the study are compared with the t-profiles of the four clinically established therapeutic drug groups. The complete tables of similarity correlation coefficients are shown in appendix C, and the graphic interpretation (mean of RR and RT) for each drug is shown in figure 7, 8, 9, and 10.

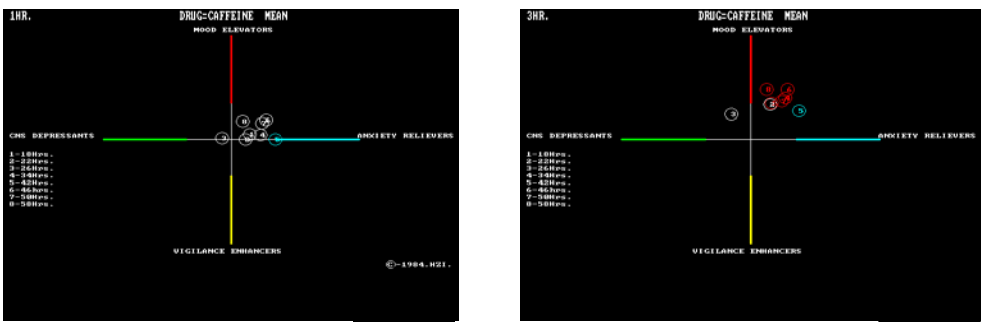

Figure 7. One and three hours database (1HR & 3HR) similarity correlation coefficients for caffeine group. All QEEG sessions did not classify caffeine as psychostimulant (vigilance enhancer). In the three hours database, there is a low correlation with mood elevators, mainly on the later sessions. None of the classifications were significant.

Figure 8. One and three hours database (1HR & 3HR) similarity correlation coefficients for dextroamphetamine group. The group did not show effective correlations. The highest similarities were with mood elevators in the three hours database after the second session. None of the classifications were significant.

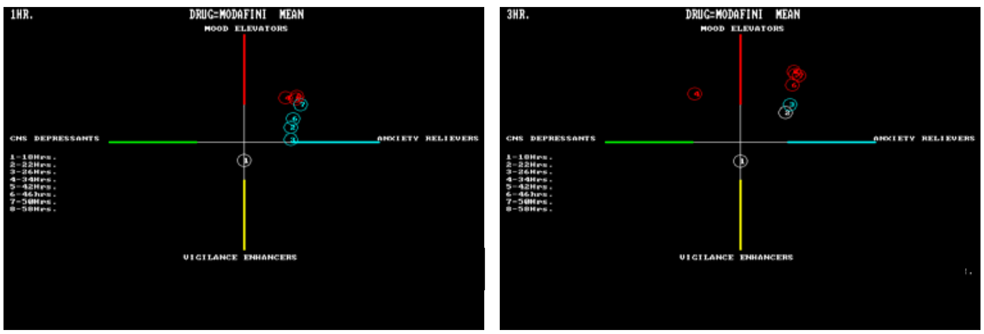

Figure 9. One and three hours database (1HR & 3HR) similarity correlation coefficients for modafinil group. Modafinil had low similarity coefficients with anxiety relievers in the one hour database and with mood elevators in the one and three hours database. None of the classifications were significant.

Figure 10. One and three hours database (1HR & 3HR) similarity correlation coefficients for placebo group. Placebo group had some similarity with antidepressants in the one hour database and some with CNS depressants in the three hours database. None of the classifications were significant.

Drugs with similar QEEG profiles (shapes) tend to have similar therapeutic effects. The similarity of the compound (first choice classification) was determined when the correlation coefficient of the profile belonging to the drug under investigation was greater than 0.35 for both RR and RT, when at least one of them had a correlation coefficient greater than 0.75 and when neither of the two correlation coefficients was negative. None of the drug groups classified with the required potency as a psychostimulant. In fact, they did not significantly classify in any of the therapeutic groups. There was, however, a tendency to classify under the thymoleptic-antidepressant group with low correlation coefficients. This was primarily noticed on the three hours database and was produced because of sleep deprivation effects rather than pharmacological effects.

QEEG drug-induced changes (three leads and four frequency bands)

The measures of the 20 frequency bands were collapsed into four frequency bands to generate delta (1.3 to 3.5 Hz), theta (3.5 to 7.5 Hz), alpha (7.5 to 13.0 Hz), and beta (13.0 Hz and up) activities for an occipital (O2), central (CZ), and frontal (FZ) electrode.

In order to determine whether any of the stimulants (caffeine, dextroamphetamine, and modafinil) and a 2-hr nap produced significant systematic changes on delta, theta, alpha, and beta bands throughout 87 hr of extended wakefulness, the QEEG changes from baseline to 18, 22, 26, 34, 42, 46, 50, 58, 66, 74, and 82 hr of wakefulness with six doses of the stimulants (or placebo) were calculated for each subject in terms of t-values. Drug-induced changes in each individual subject in each time period were created, and subsequently, drug-induced changes for each drug group were evaluated using t-statistics. The univariate t-statistic is useful only to determine and to observe trends, because the use of fragmented univariate tests could lead to a greatly inflated overall type I error rate.

As shown in tables 1 and 2, the caffeine group seemed to have a better response than all other groups showing less significant changes along frequency bands, time periods, and analyzed leads. There were no systematic increases of delta or theta activities, except for delta at FZ after 58 hr of sleep deprivation. Alpha activity attenuated at O2 after 42 hr and at CZ after 50 hr only for RR. FZ significantly dropped alpha activity after 46 hr of being awake. Caffeine also produced some isolated increases of beta.

While the modafinil group showed significant systematic increases of delta and decreases of alpha, they only occurred after 46 hr of sleep deprivation at CZ and FZ and after 50 hr at O2. The modafinil group produced no changes on theta or beta activities.

The dextroamphetamine and placebo groups had nearly a continuous significant decrease of alpha activity throughout all time periods at the three analyzed leads. The highest systematic and significant increase of delta was recorded at CZ and FZ. O2 shows fewer and more inconsistent increases of delta. Similar to the other drugs, the dextroamphetamine and placebo groups produced very small and unorganized changes on theta or beta activities. The complete series of graphics for all electrodes and sessions is shown in appendix D.

Table 1.
Caffeine and dextroamphetamine drug and sleep-deprivation induced changes from baseline to each subsequent time period based on t-values.

	Caffeine								Dextroamphetamine							
	Delta		Theta		Alpha		Beta		Delta		Theta		Alpha		Beta	
O2	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT
18 hr					-								-	-		
22 hr													-	-		++
26 hr													--	--	+	
34 hr													--	--		
42 hr					-		++			+			--	--		
46 hr					-								--	--		
50 hr					-				+				--	--		
58 hr							++		++	++			--	--		
66 hr					-								--	--		
74 hr					-								--	--		
82 hr					--					++			--	--		
Total					7		2		2	3			11	11	1	1

	Caffeine								Dextroamphetamine							
	Delta		Theta		Alpha		Beta		Delta		Theta		Alpha		Beta	
CZ	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT
18 hr			-											-		
22 hr													-		+	
26 hr										++	-		-	--	+	
34 hr									++				--	--	+	
42 hr							+		++	++			-	--		
46 hr									++	+			--	--		
50 hr					-				++	++			--	--		
58 hr					-				++	++			--	--		
66 hr					--				++	++			--	--		
74 hr									++	++			--	--		
82 hr									++	++			--	--		
Total			1		3		1		8	8	1		10	10	3	

	Caffeine								Dextroamphetamine							
	Delta		Theta		Alpha		Beta		Delta		Theta		Alpha		Beta	
FZ	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT
18 hr			--				++									
22 hr													-			
26 hr							+						-	--		
34 hr	+								+				--			
42 hr								++					-	--		
46 hr					--				++	+			--	--		
50 hr					--	--			+	+			--	--		
58 hr		++				--			++	++			--	--		
66 hr	++				--				++	++			--	--		
74 hr	++				--	--			++	++			--	--		
82 hr	++	++			--	--			++	+			--	--		
Total	4	2	1		5	4	2	1	7	6			10	8		

Note: Rows depict the time periods (hr awake), and columns show the caffeine and dextroamphetamine groups with their four frequency bands subdivided by RR and RT. + Increase $p < .05$; ++ Increase $p < .01$; - Decrease $p < .05$; -- Decrease $p < .01$

Table 2.

Modafinil and placebo drug and sleep-deprivation induced changes from baseline to each subsequent time period based on t-values.

	Modafinil								Placebo							
	Delta		Theta		Alpha		Beta		Delta		Theta		Alpha		Beta	
O2	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT
18 hr																
22 hr													-	-		
26 hr													--	--		
34 hr									+				--	--		
42 hr						--			++				--	--		
46 hr					-	--			+	++			--	--		
50 hr	+								+				--	--		
58 hr		++			-	--			+		+		--	--		
66 hr	++				-	--							--	--		
74 hr	+	++			-	--							--	--		
82 hr	+	+			-	--							--	--		
Total	4	3			5	6			5	1	1		11	11		
	Modafinil								Placebo							
	Delta		Theta		Alpha		Beta		Delta		Theta		Alpha		Beta	
CZ	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT
18 hr																
22 hr		+			-	-			+				--	-		
26 hr									++				--			
34 hr									++	+			--			
42 hr						-			++	++			--	-		
46 hr	+	++			--	--			++	++			--	--		
50 hr	++	+							++	++			--	-		
58 hr	++	++			-	--			++		+		--	-	--	
66 hr	++				--	--			++	++			--	--		
74 hr	++	++			-	--						-	--			
82 hr	++	++			--	--			++	+			--	-		
Total	6	6			6	7			9	6	1	1	10	7	1	
	Modafinil								Placebo							
	Delta		Theta		Alpha		Beta		Delta		Theta		Alpha		Beta	
FZ	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT	RR	RT
18 hr																
22 hr		+			-	-				+			--			
26 hr													--			
34 hr									+				--			
42 hr	+					-							--	-		
46 hr	++	++			--	--			++	++			--	--		
50 hr	++	++			-	--			++	++		-	--	--		
58 hr	++	++			--	--			++	++			--	--	-	
66 hr	++	+			--	--			++	++			--	--		
74 hr	++	++			-	--							--	-		+
82 hr	+	++			--	--				++			--	--		
Total	7	7			7	8			5	6		1	10	7	1	1

Note: Rows depict the time periods (hr awake), and columns show the modafinil and placebo groups with their four frequency bands subdivided RR and RT.; + Increase $p < .05$; ++ Increase $p < .01$; - Decrease $p < .05$; -- Decrease $p < .01$

Detection of drug effects

To remove variability among subjects in the same group and to determine performance trends over the sleep deprivation cycle, a repeated measure analysis of variance (ANOVA) was carried out with four drug group levels (caffeine 200 mg, dextroamphetamine 5 mg, modafinil 100 mg, and placebo) as between-subjects factor, and the eight QEEG sessions (18, 22, 26, 34, 42, 46, 50, and 52 hr) were entered as a repeated measure. Each of these QEEGs was subtracted from the baseline QEEG to create score changes on delta, theta, alpha, and beta bandwidths at O2, CZ, and FZ. The analysis was performed on the overall recording time using both RR and RT segments. In checking assumptions, Box's M and Mauchly's test of sphericity were used. To circumvent the compound symmetry violation in all variables, we used lower-bound epsilon adjustment, which represents the most conservative approach.

<u>Delta activity</u>

The different pharmacological conditions resulted in distinct changes in delta activity. Drug main effects and QEEG session effects were at all three electrodes. The drug effects at O2, $F(3, 52) = 3.01$, $p = .038$; CZ, $F(3, 52) = 7.51$, $p < .001$; and FZ, $F(3, 52) = 3.56$, $p = .02$ were tested using Tukey HSD post-hoc comparisons. This test revealed significant differences between modafinil and placebo at O2 and CZ and between caffeine and placebo at CZ and FZ. Caffeine was also discriminated with dextroamphetamine at CZ. The session effects at O2, $F(1, 52) =$ 6.39, $p = .015$; CZ, $F(1, 52) = 26.81$, $p < .001$; and FZ, $F(1, 52) = 52.49$, $p < .001$ were primarily due to a significant linear increase in delta activity from the first to the last sessions of the sleep deprivation cycle. In addition, there was a session by drug interaction at CZ, ($F = 3.36$, $p =$ .026). The mean score changes for O2, CZ, and FZ are shown in figure 11.

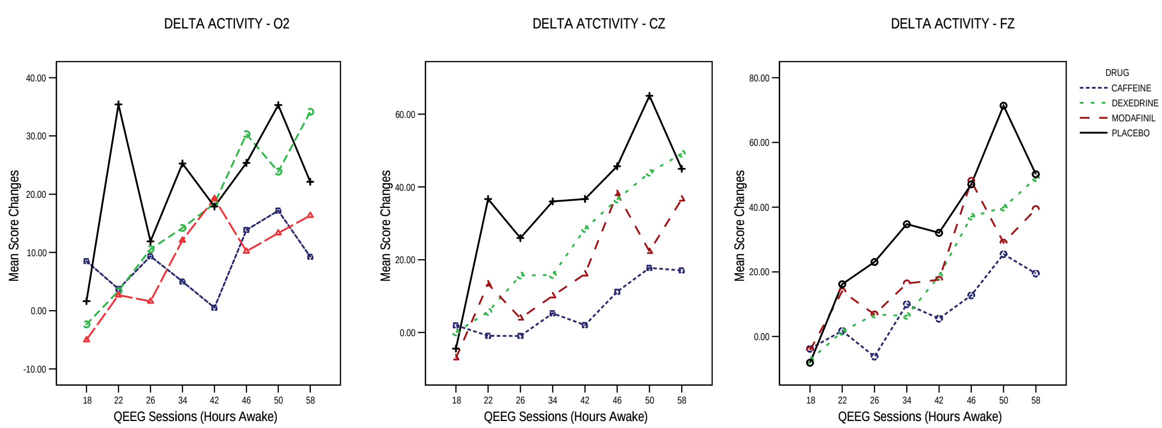

Figure 11. Mean score changes for delta activity at O2, CZ, and FZ.

Alpha activity.

There was no drug main effect in the frontal electrode, FZ. However, alpha activity showed significant drug effects at O2, $F(3, 52) = 3.12$, $p = .034$ and CZ, $F(3, 52) = 3.61$, $p = .019$. Post-hoc analysis disclosed that dextroamphetamine is significantly different from modafinil at O2 and significantly different from caffeine at CZ. There were significant session effects at O2, $F(1, 52) = 27.14$, $p < .001$; CZ, $F(1, 52) = 34.90$, $p < .001$; and FZ, $F(1, 52) = 44.94$, $p < .001$, produced by significant linear and quadratic decreases in all leads. The session by drug interactions at CZ, $F = 3.51$, $p = .022$ and at FZ, $F = 2.39$, $p = .042$ were essentially the result of high variability over time among the four groups. Figure 12 depicts the score changes for alpha over the sessions.

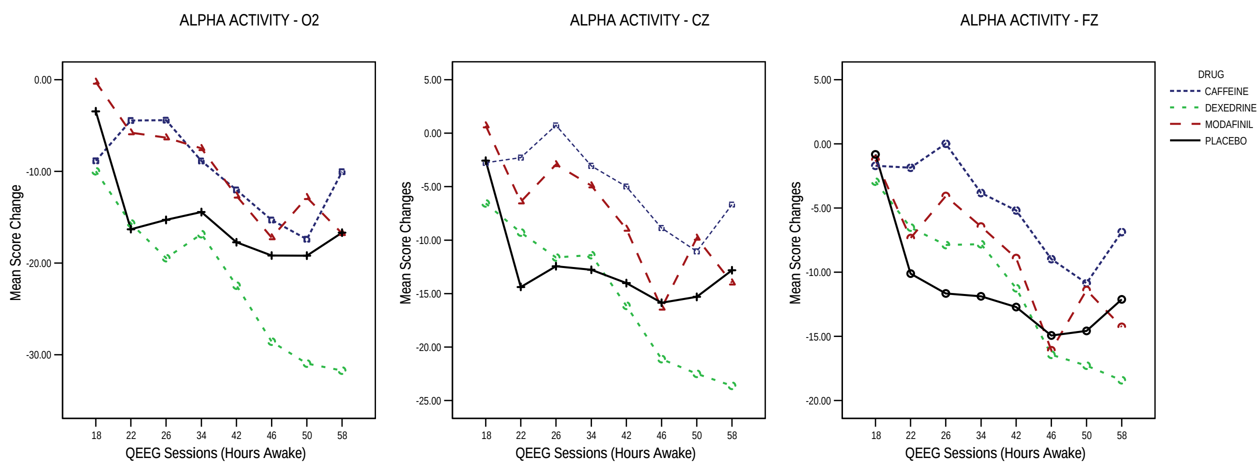

Figure 12. Mean score changes for alpha activity at O2, CZ, and FZ.

Theta activity

Theta activity did not show drug effects or interactions at any of the three leads. The only significant change was a session effect at O2, $F(1, 52) = 4.84$, $p = .032$, due to a constant linear increase across all sessions. Means are shown in figure 13.

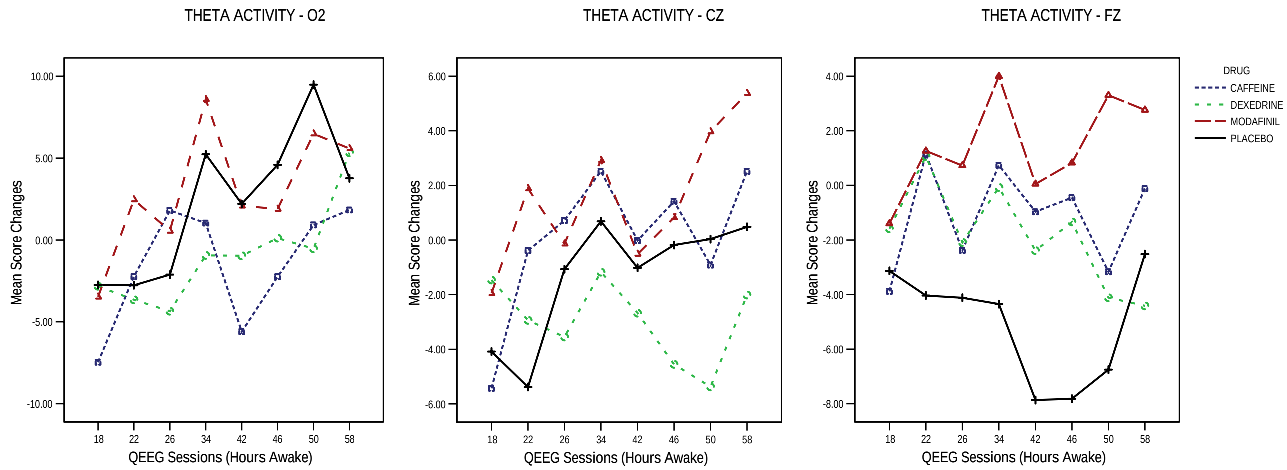

Figure 13. Mean score changes for theta activity at O2, CZ, and FZ.

Beta activity

Similar to theta activity, beta did not produced drug effects or interactions at any electrode. There were, however, session effects at CZ, $F(1, 52) = 4.35$, $p = .042$ and FZ, $F(1, 52) = 9.89$, $p = .003$, due to a significant linear decrease in both leads. Beta activity is shown in figure 14.

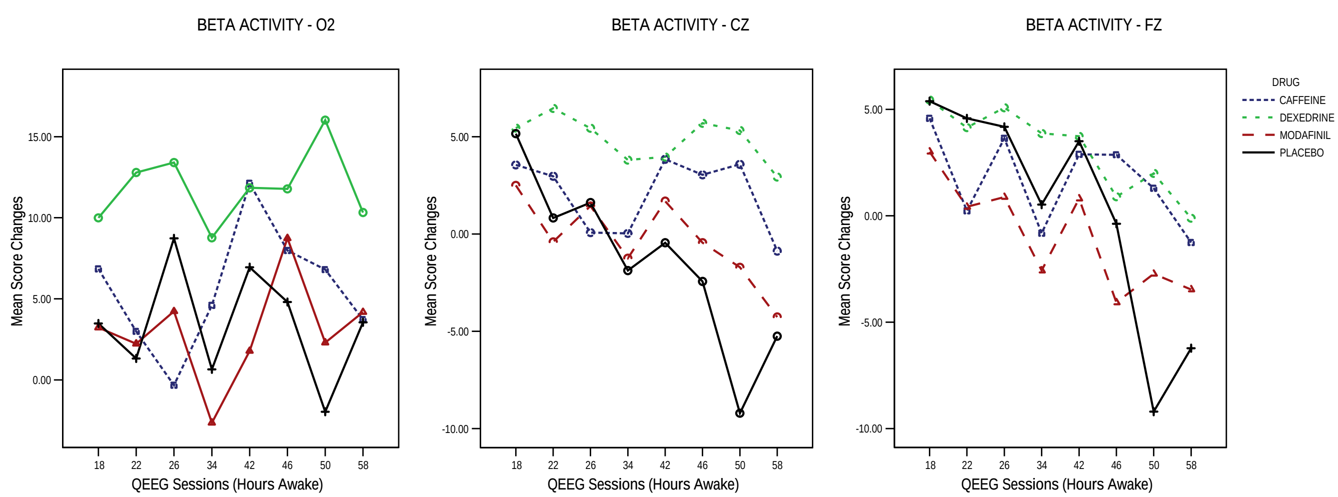

Figure 14. Mean score changes for beta activity at O2, CZ, and FZ.

Detection of nap effects

To assess whether a nap attenuates the sleep-like patterns of the QEEG, we created separate difference variables by subtracting each subject's scores observed in adjacent sessions. The QEEG data from the two post napping sessions (74 and 82 hr awake) was used to compare the last session prior to napping (66 hr) using a repeated measure ANOVA. Four levels of drug groups were entered as between-subjects and three sessions (66, 72, and 82 hr) as repeated measures. Significant drug effects were found on alpha activity at O2, $F(3, 52) = 4.05$, $p = .012$ and at CZ, $F(3, 52) = 3.92$, $p = .014$. Dextroamphetamine had significant differences with caffeine and placebo at O2 and with caffeine at CZ. The central electrode CZ also had significant drug effects in delta and theta activities, $F(3, 52) = 2.92$, $p = .042$ and $F(3, 52) = 3.64$, $p = .018$, respectively. These were the results of differences between caffeine and dextroamphetamine. Three session effects, for delta at FZ, $F(2, 52) = 3.96$, $p = .027$ and CZ, $F(2, 52) = 3.87$, $p = .026$ and for beta at CZ, $F(3, 52) = 3.61$, $p = .03$, were produced by differences between the 66 hr versus the 74 hr sessions and the 66 versus the 82 hr sessions. Session by drug interactions were detected at CZ for delta, $F = 2.73$, $p = .016$ and beta, $F = 2.54$, $p = .027$. Mean score changes for delta, theta, and alpha activities are shown in figure 15.

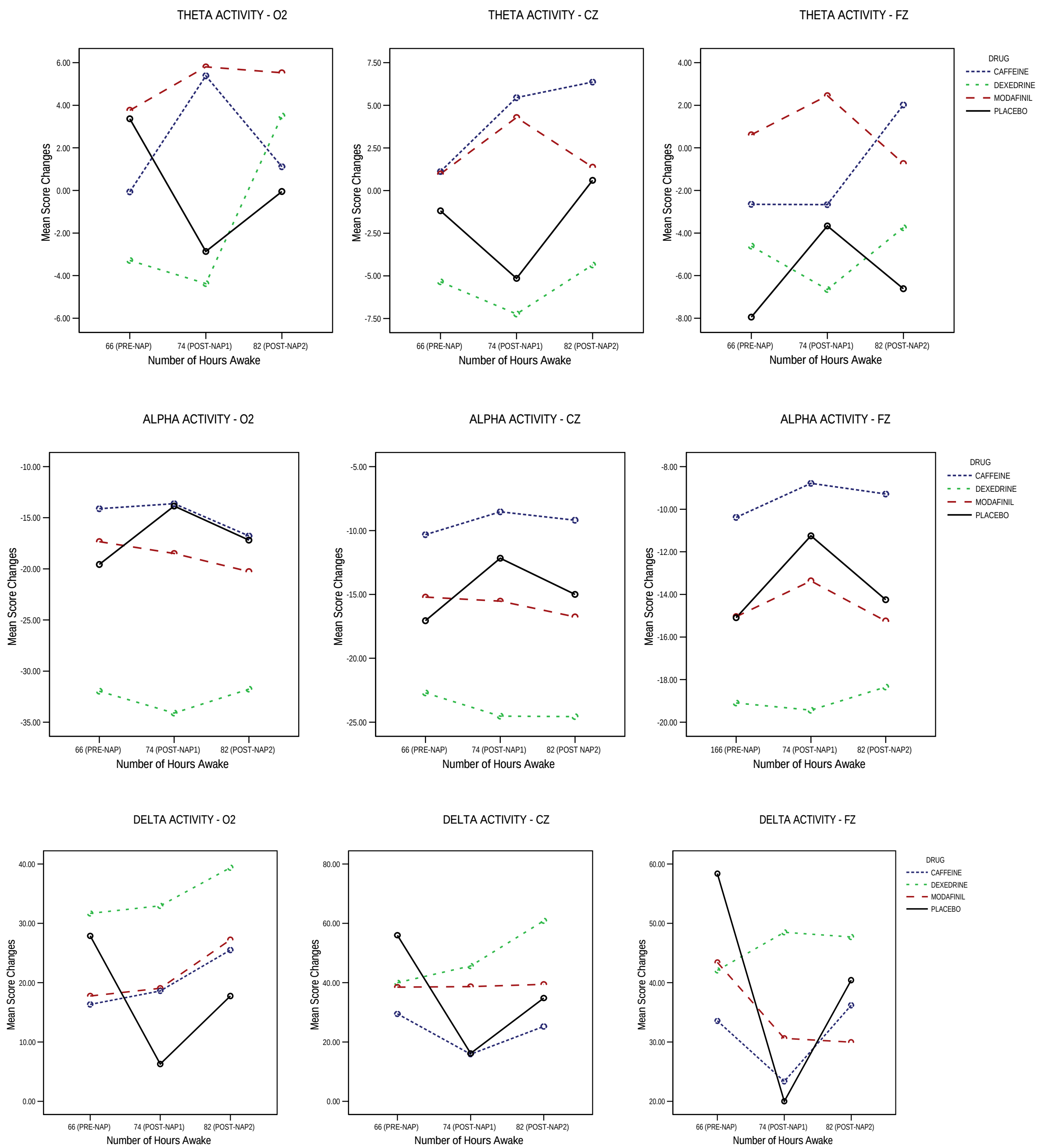

Figure 15. Mean score changes for delta, theta, and alpha activity at O2, CZ, and FZ for the pre- and post- napping sessions.

Discussion

It is expected that drug induced changes with psychostimulants will produce a decrease of the slow brain waves and an increase in alpha activity (Itil, Cardillo, and Cig, 2002). However, similarity correlation coefficients with a QEEG psychostimulants database did not show significance at the occipital lead. In fact, there were nearly no decreases of slow waves and no increases of alpha activity throughout the entire sleep deprivation cycle in any of the three analyzed leads. This could be attributed in part to the sleep deprivation factor and to the fact that all recording sessions were performed between 30 and 40 minutes after the drug administration. Considering that the time for maximum drug concentration in plasma is 1.5 hr for caffeine, 3 hr for dextroamphetamine, and 2-4 hr for modafinil, QEEGs started to measure residual drug effects (due to elimination halftime) after the second dose, but actual peak CNS changes were never measured. The relatively low similarity with mood elevators was produced by the sleep deprived brain patterns. Alpha attenuation, and an increase in delta and theta, is considered one of the first signs of falling asleep (Pigeau, 2001), and mood elevator QEEG patterns are characterized by a decrease in alpha and in some cases also an increase in slow and/or fast frequency (Itil, Cardillo, and Cig, 2002).

The results from the repeated measure ANOVA during the drug sessions tend to confirm the trends observed on the drug induced changes section using t-statistics. Theta and beta activities were not sensitive to pilot fatigue due to sleep deprivation or drug effects. The most predominant changes were established in delta and alpha activities showing session effects at all electrodes with linear increase on delta and with linear and quadratic decrease on alpha. Delta activity showed significant between-subject responses at the three leads and alpha at the occipital and central leads. Also, all three significant interactions were produced at these activities mainly in the central and frontal regions.

Caffeine produced less significant changes from baseline and was clearly differentiated from placebo and dextroamphetamine. Caffeine attenuated the slow waves and slightly increased beta activity, consistent with a recent study on the effects of caffeine on the brain (Hammond, 2003). Similar to caffeine, modafinil produced fewer changes from baseline on delta and theta activities during the first 34 hr and on alpha activity during the first 42 hr of wakefulness. Modafinil showed virtually no changes on beta activity throughout the entire cycle and showed improvement on delta when compared to placebo at O2 and CZ but not on theta. These results partially agree with a similar previous modafinil study (Caldwell et al., 2000), which showed delta and theta improvements at CZ. However, they used double the dose (200 mg) and a shorter sleep deprivation period (40 hr). The increase of delta activity under dextroamphetamine was similar to the increase seen with placebo and the decrease on alpha even greater than the decrease seen on placebo. These outcomes contradict the electroencephalographic results established in several studies with dextroamphetamine which reported significant attenuation of slow-wave increase and a more normal alpha activity (Caldwell and Hall, 2001). These four studies each used 10 mg of dextroamphetamine (vs. 5 mg in the present study); three studied shorter periods of sleep deprivation (40 hr) and one studied 64 hr.

The present study showed increases in delta activity due to the sleep deprivation factor; an increase in delta activity is primarily associated with sleep in normal adults (Ray, 1990). It is also known that sleepiness and fatigue elevates slow-wave activities (Pigeau, Heselgrave, and Angus, 1978). However, this study revealed virtually no increases in theta activity across the sleep deprivation cycle, for all groups, including placebo. An increase in theta activity alone has been associated with generalized performance decrements on cognitive tasks (Belyavin and Wright, 1987) and reduced speed of response to incoming stimuli (Ogilvie and Simons, 1992). The lack of significant changes in theta activity may represent effort levels consistently across all groups. For example, motivation can counteract the effect of sleep deprivation, since the adverse effects of sleep loss on performance and behavior are very labile and can easily be cancelled by suitably arousing conditions (Wilkinson, 1992). Furthermore, it was also shown that monetary rewards for good performance maintained baseline levels for 36 hr without sleep (Horne and Pettit, 1985).

Summary

The primary objective of this part of the investigation was to identify the extent and distribution of electrophysiological changes induced by 87 hr of continuous sleep deprivation, using three different stimulants with placebo and napping. The main differences during the pre- and post-nap sessions were between caffeine and dextroamphetamine. Considering that the two post-nap sessions for the QEEG were more than 5 and 13 hr after the nap, we are not measuring an immediate, but rather a longer term effect due to the nap. A pragmatic but subjective observation is that the placebo group, as represented in figure 15, depicts slow-wave decreases and alpha increases at all electrodes (except theta at FZ), suggesting a better temporary recovery of at least 5 hr.

In conclusion, we found that after 87 hr, all drug and control groups showed EEG signs of sleep deprivation: increases in slow-waves (mainly delta) and decreases in alpha waves. The electrophysiological effects of sleep deprivation are reversed during the initial 42 hr, with smaller increases in delta activity by caffeine, modafinil, or dextroamphetamine, and less deterioration of alpha activities for caffeine and modafinil when compared to baseline levels. Caffeine and modafinil appeared to have the greatest degree of effect with respect to producing delays on alpha activity deterioration. Alpha activity remained close to baseline levels for the first 46 hr. A marked deterioration of alpha right after the second dose was observed (22 hr) in the dextroamphetamine and placebo groups.

The multi-lead evaluation shows that the dynamic brain mapping of subjects from all drug groups had similar (normal) QEEG patterns when well rested and without drugs (baseline QEEGs). When looking at the occipital lead in the placebo group alone, it can be confirmed that sleep-deprived subjects have different QEEG spectrums (profiles) than those not sleep-deprived. Interestingly, those QEEG profiles for the sleep-deprived subjects are opposite to the QEEG changes induced by psychostimulants in well rested healthy volunteers. In order to determine the best adaptability to sustained operations, future studies are needed to establish the CNS effective doses for the drugs based on the magnitude of the deprivation period. Individual

differences that exist for personality features, physiological reasons, and circadian typology may be accounted for by titrating drug dose to both performance and electrophysiological measures.

Additional analysis of this study data could systematically correlate cognitive tasks and QEEG data for each pharmacologic intervention. Through QEEG, measures are available that may be used to directly relate the brain effects of the drug to the performance effects.

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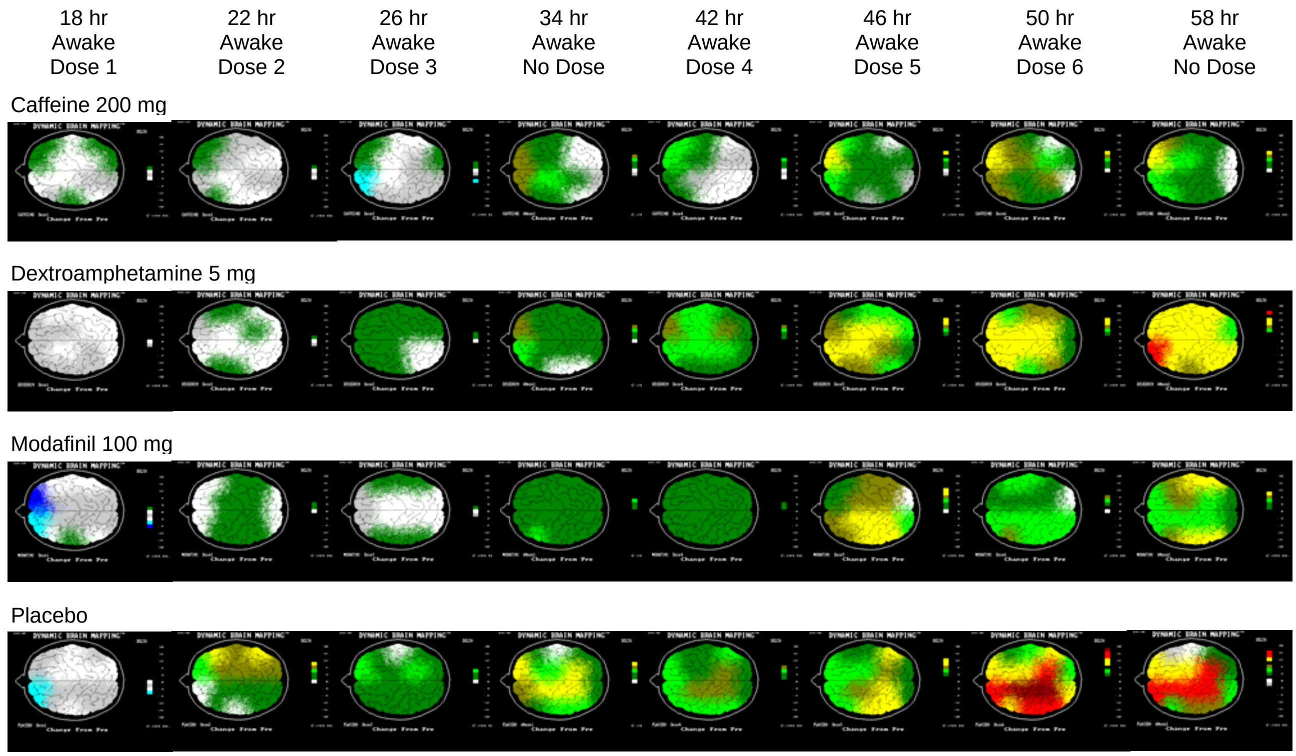
Appendix A.

Dynamic brain mapping (changes from baseline).

Delta activity



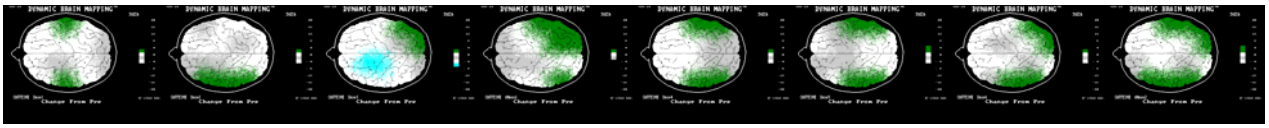
Color code: White indicates no changes in comparison to pre-drug. Dark green to light green to yellow to red indicates increase of activity. Light blue to dark blue to violet indicates decrease of activity.

Figure A-1. During the first 26 hr of wakefulness, caffeine shows almost no changes on delta activity with only a slight increase on the right frontal area. Slight to moderate general increases are produced as the sleep deprivation cycle progress, with highest increases in the frontal area. Dextroamphetamine begins to show overall moderate increases of delta after the third dose (26 hr awake), with moderate to marked increases after 34 hr of being awake. Modafinil produced a slight decrease of delta in the frontal area after 18 hr awake and a general moderate increase after 26 hr. At 22 hr of wakefulness and throughout the rest of the sleep deprivation period, placebo group shows moderate to marked increases of delta activity on the entire brain.

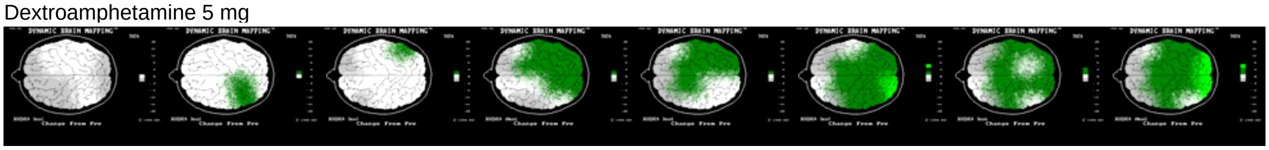
Theta activity

18 hr Awake Dose 1	22 hr Awake Dose 2	26 hr Awake Dose 3	34 hr Awake No Dose	42 hr Awake Dose 4	46 hr Awake Dose 5	50 hr Awake Dose 6	58 hr Awake No Dose

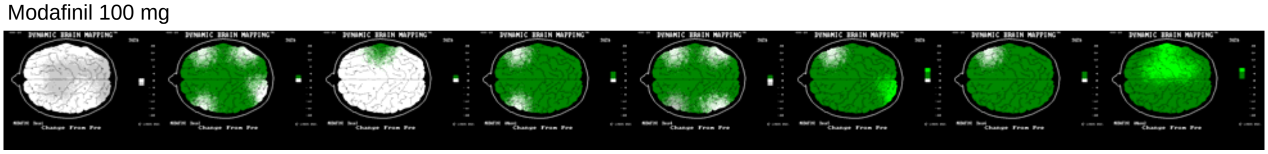
Caffeine 200 mg



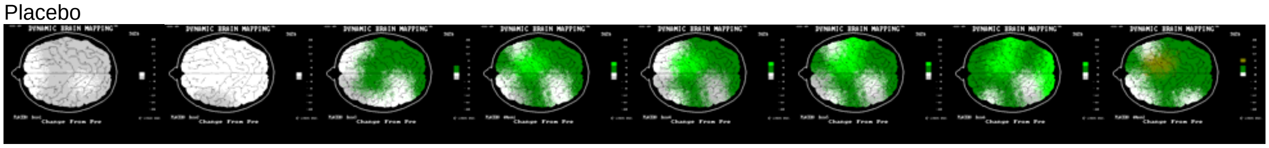
Dextroamphetamine 5 mg



Modafinil 100 mg



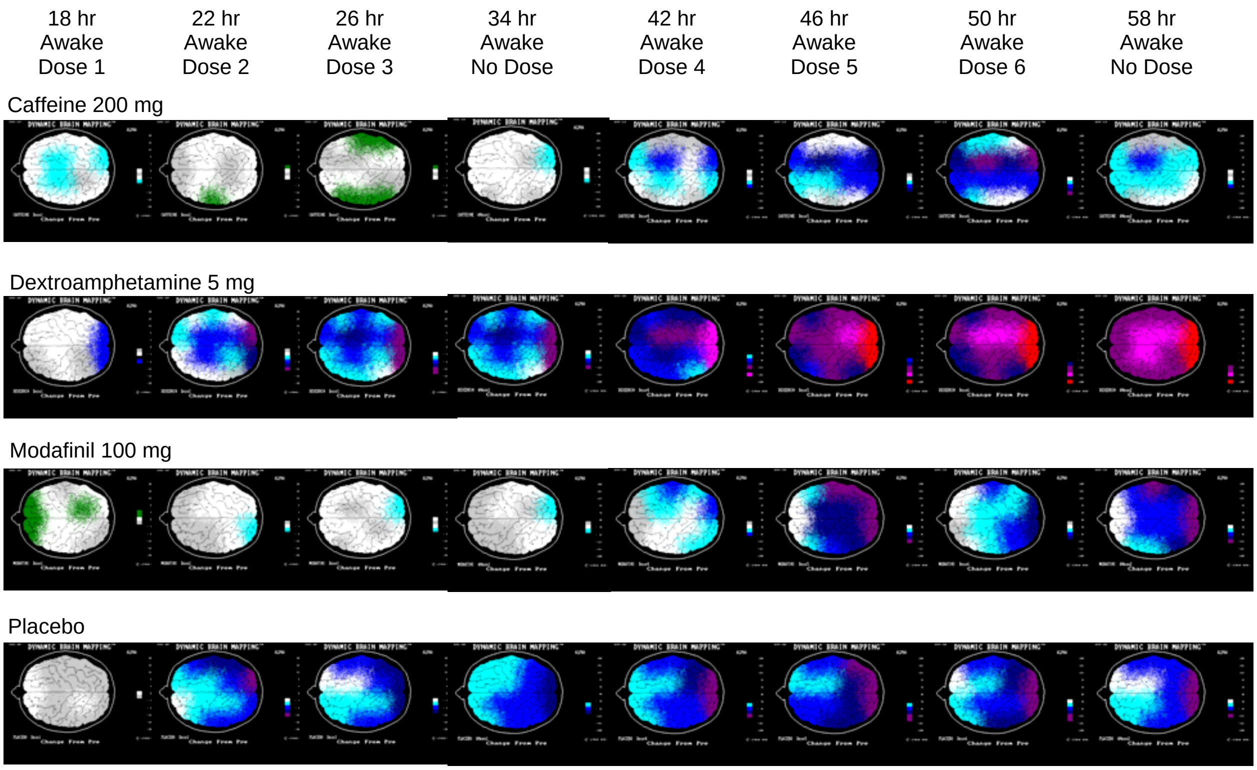
Placebo



<u>Color code:</u> White indicates no changes in comparison to pre-drug. Dark green to light green to yellow to red indicates increase of activity. Light blue to dark blue to violet indicates decrease of activity.

Figure A-2. Caffeine produced nearly no changes on theta activities with the exception of a slight temporal increase after 34 hr of being awake. Dextroamphetamine and placebo show more generalized slight increases after 34 hr of sleep deprivation. Modafinil produced no changes right after the first and third doses and produced an overall slight increase of theta activity in any of the other time points.

Alpha activity



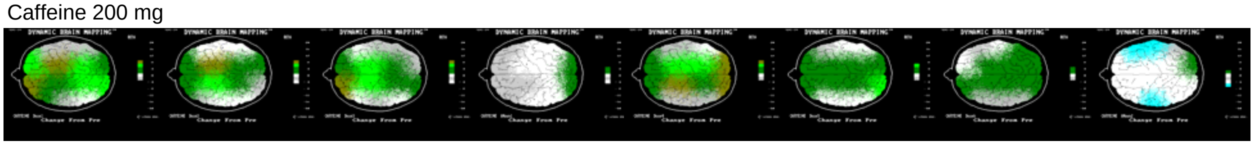
<u>Color code:</u> White indicates no changes in comparison to pre-drug. Dark green to light green to yellow to red indicates increase of activity. Light blue to dark blue to violet indicates decrease of activity.

Figure A-3. Caffeine and modafinil produced virtually no changes on alpha activity up until 42 hours of sleep deprivation. At 42 hr, there is a slight to moderate decrease, particularly on the occipital area and a moderate to marked decrease from 46 to 58 hr of wakefulness. Placebo and dextroamphetamine groups show a steady, moderate to marked decrease of alpha throughout the entire deprivation period. Dextroamphetamine shows the highest decreases, particularly after 46 hr of being awake.

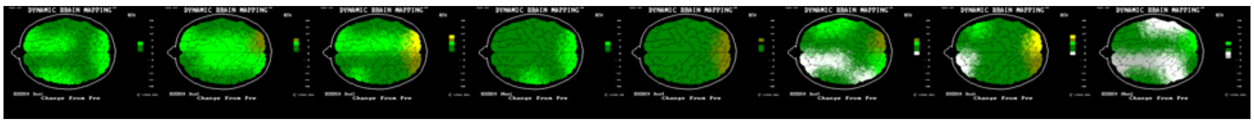
Beta activity

18 hr Awake Dose 1	22 hr Awake Dose 2	26 hr Awake Dose 3	34 hr Awake No Dose	42 hr Awake Dose 4	46 hr Awake Dose 5	50 hr Awake Dose 6	58 hr Awake No Dose

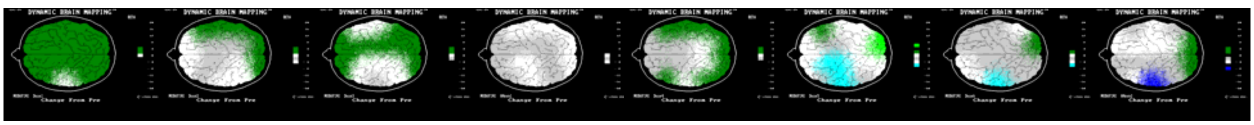
Caffeine 200 mg



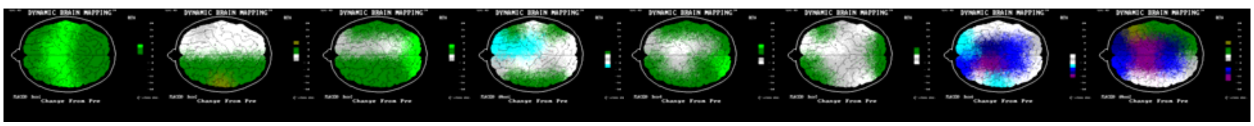
Dextroamphetamine 5 mg



Modafinil 100 mg



Placebo



<u>Color code: </u>White indicates no changes in comparison to pre-drug. Dark green to light green to yellow to red indicates increase of activity. Light blue to dark blue to violet indicates decrease of activity.

Figure A-4. There is a slight to moderate increase of beta activities for all groups during the first 26 hr, except for the dextroamphetamine group which increase throughout the entire cycle. As the sleep deprivation cycle progresses, beta increases tend to be lower, particularly on caffeine and near to baseline levels for modafinil. After 50 hr, the placebo group had a drop on the activity showing a moderate to marked decrease.

Appendix B.

Individual t-values profiles.

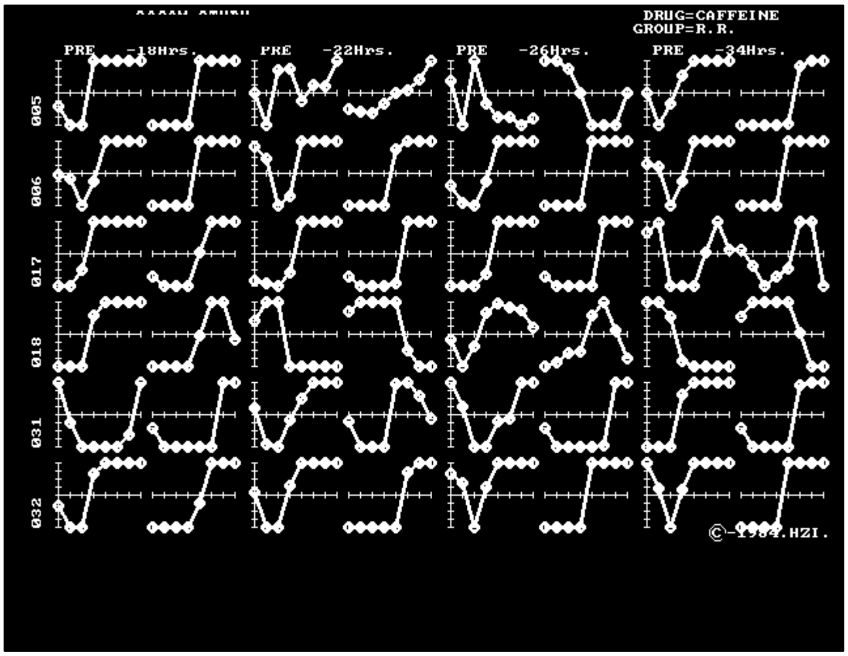


Figure B-1. Individual t-profile for the caffeine group (resting recording). Sessions 18, 22, 26, and 34 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave and the graph on the right is first derivative.

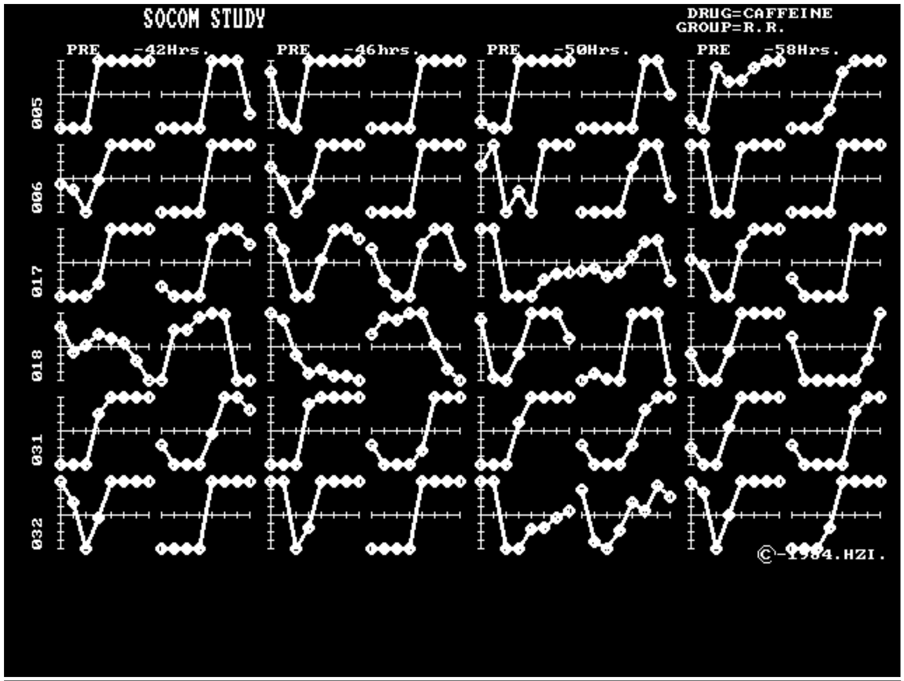


Figure B-2. Individual t-profile for the caffeine group (resting recording). Sessions 42, 46, 50, and 58 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

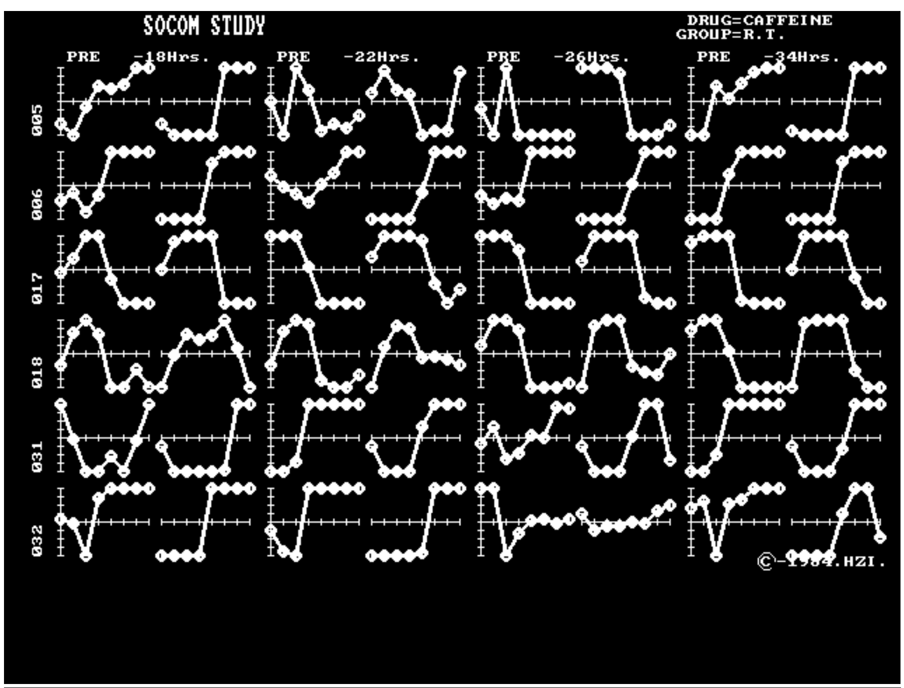


Figure B-3. Individual t-profile for the caffeine group (reaction time). Sessions 18, 22, 26, and 34 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

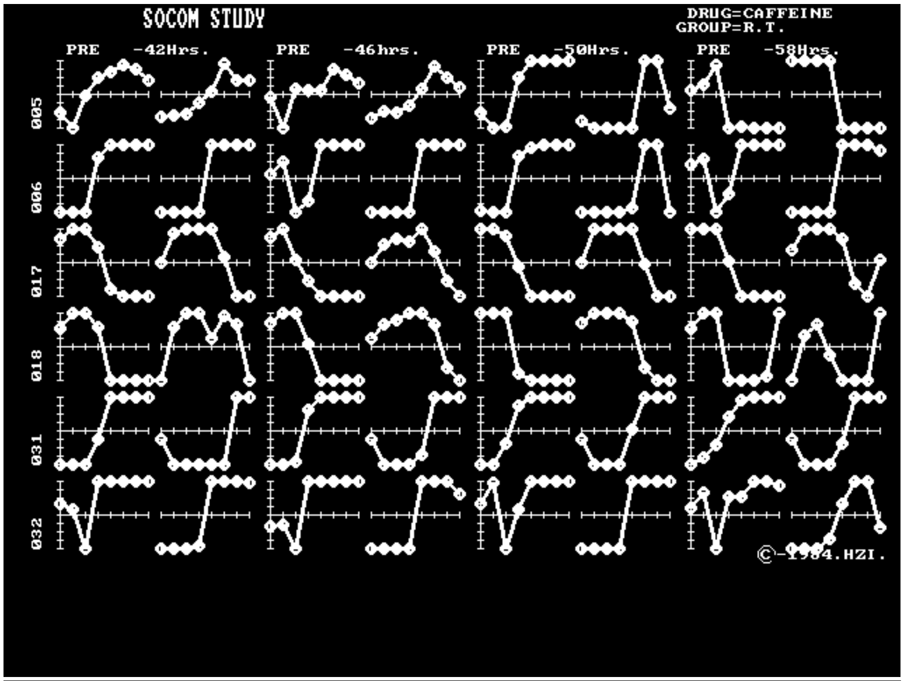


Figure B-4. Individual t-profile for the caffeine group (reaction time). Sessions 42, 46, 50, and 58 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

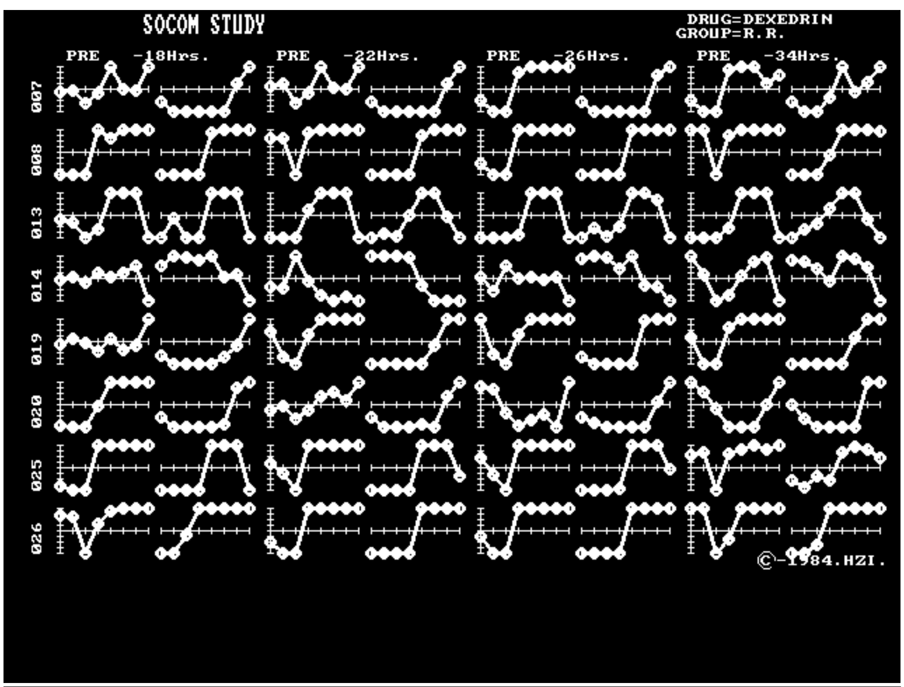


Figure B-5. Individual t-profile for the dextroamphetamine group (resting recording). Sessions 18, 22, 26, and 34 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave and the graph on the right is first derivative.

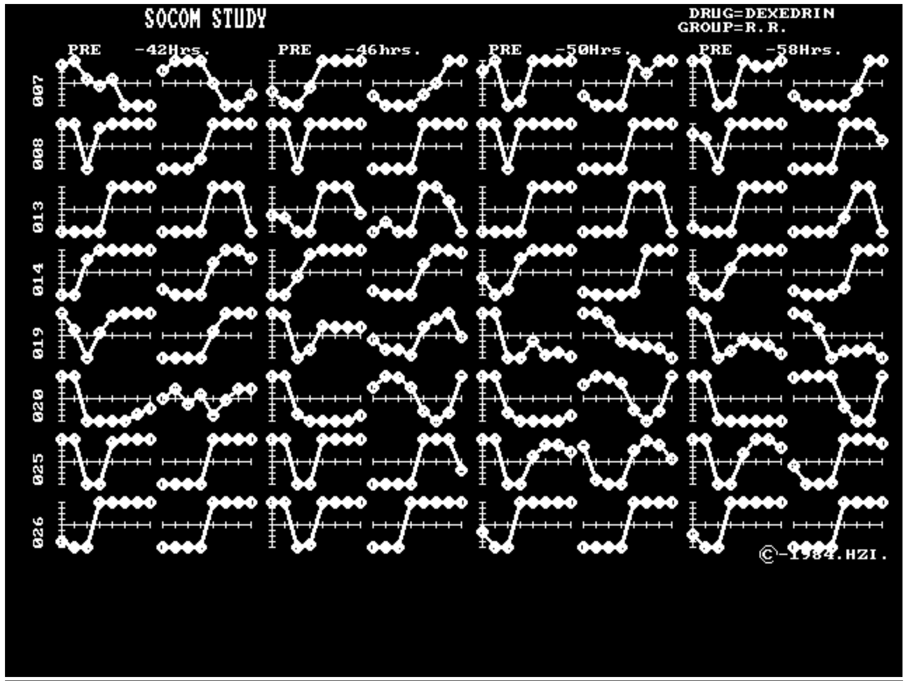


Figure B-6. Individual t-profile for the dextroamphetamine group (resting recording). Sessions 42, 46, 50, and 58 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

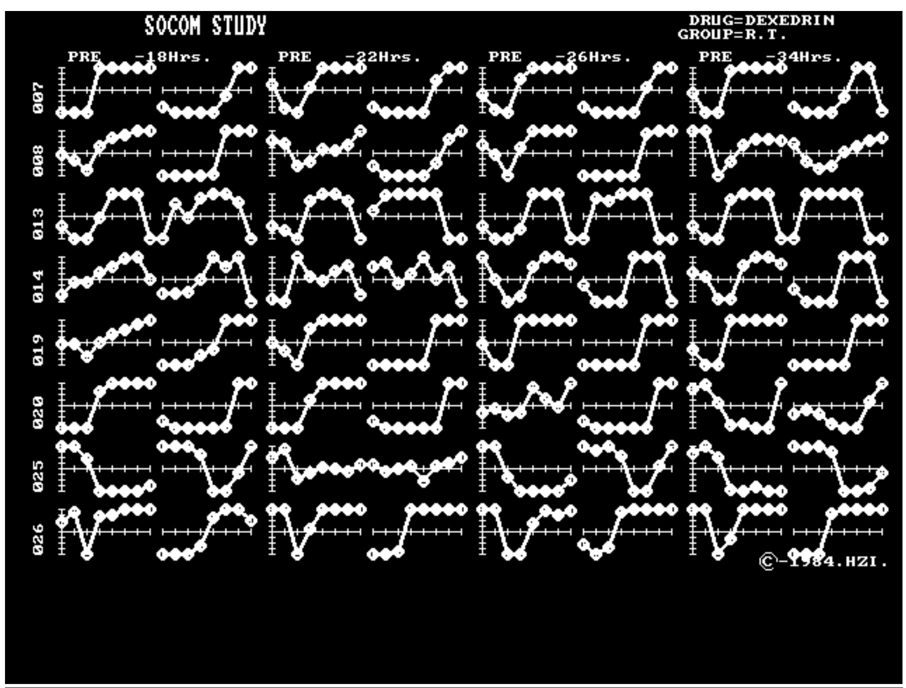


Figure B-7. Individual t-profile for the dextroamphetamine group (reaction time). Sessions 18, 22, 26, and 34 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

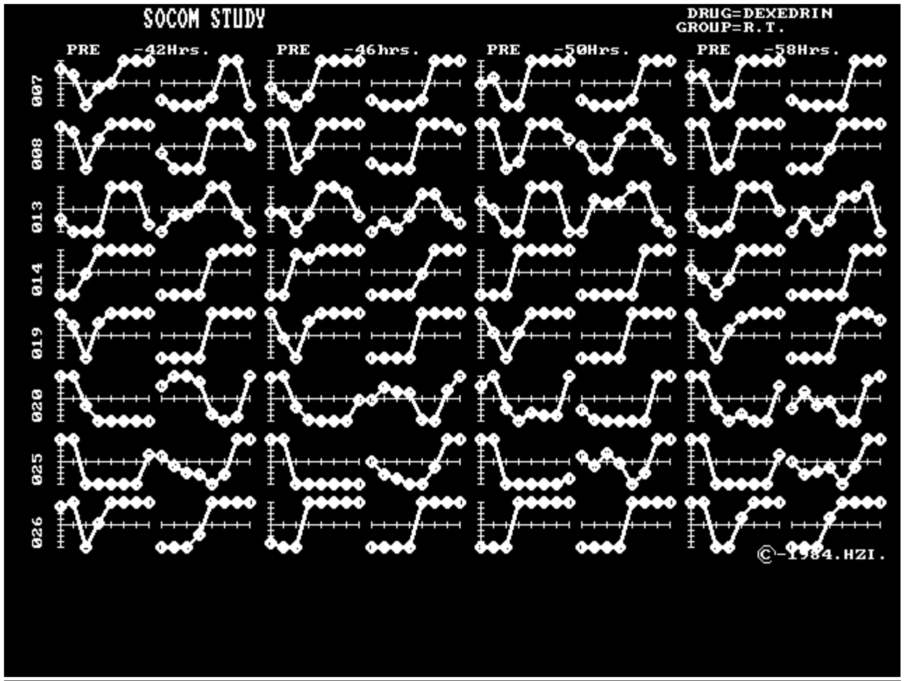


Figure B-8. Individual t-profile for the dextroamphetamine group (reaction time). Sessions 42, 46, 50, and 58 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

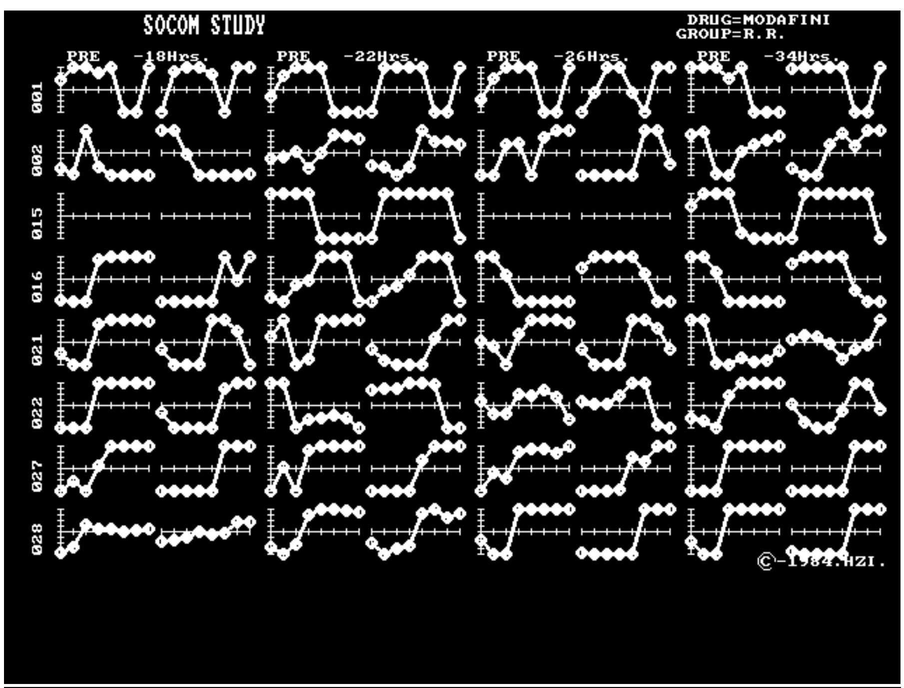


Figure B-9. Individual t-profile for the modafinil group (resting recording). Sessions 18, 22, 26, and 34 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

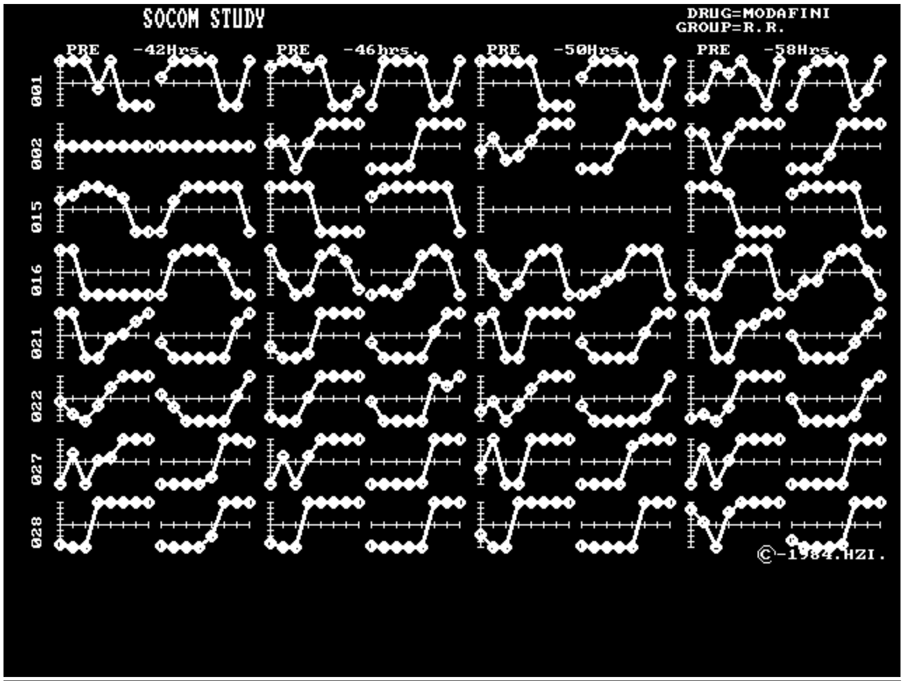


Figure B-10. Individual t-profile for the modafinil group (resting recording). Sessions 42, 46, 50, and 58 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

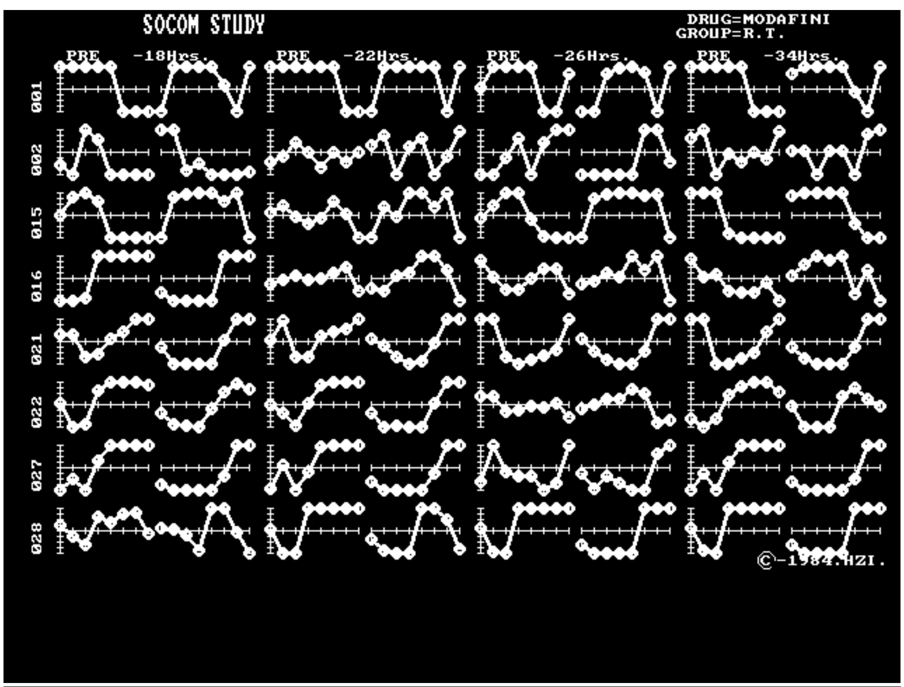


Figure B-11. Individual t-profile for the modafinil group (reaction time). Sessions 18, 22, 26, and 34 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

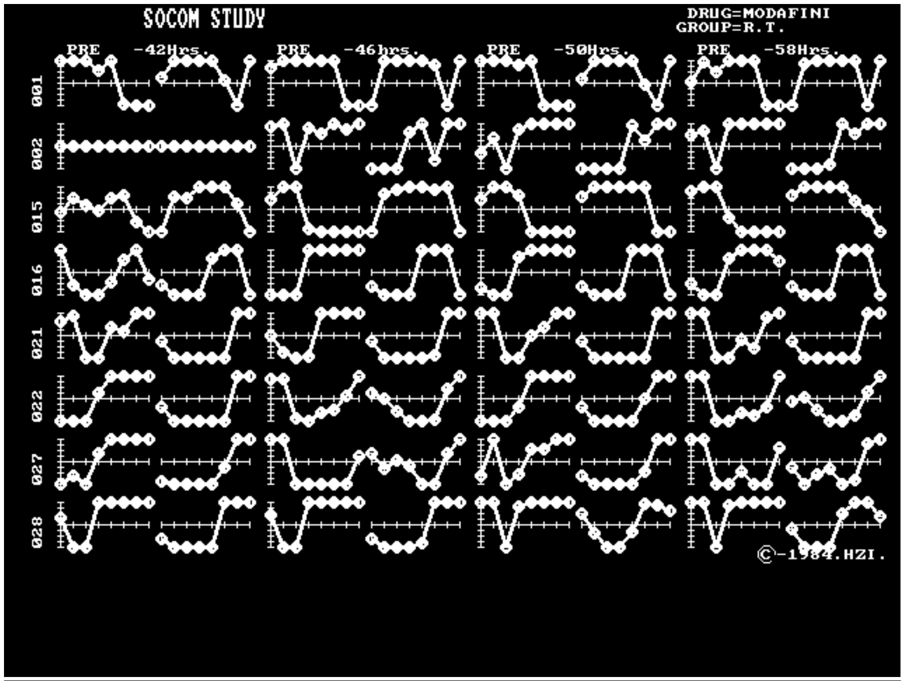


Figure B-12. Individual t-profile for the modafinil group (reaction time). Sessions 42, 46, 50, and 58 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

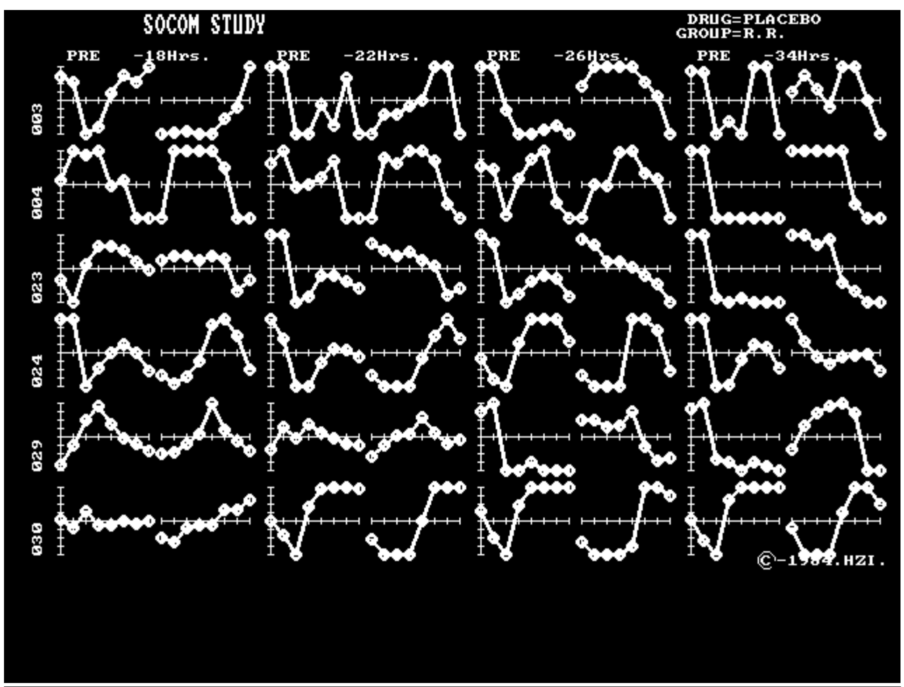


Figure B-13. Individual t-profile for the placebo group (resting recording). Sessions 18, 22, 26, and 34 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

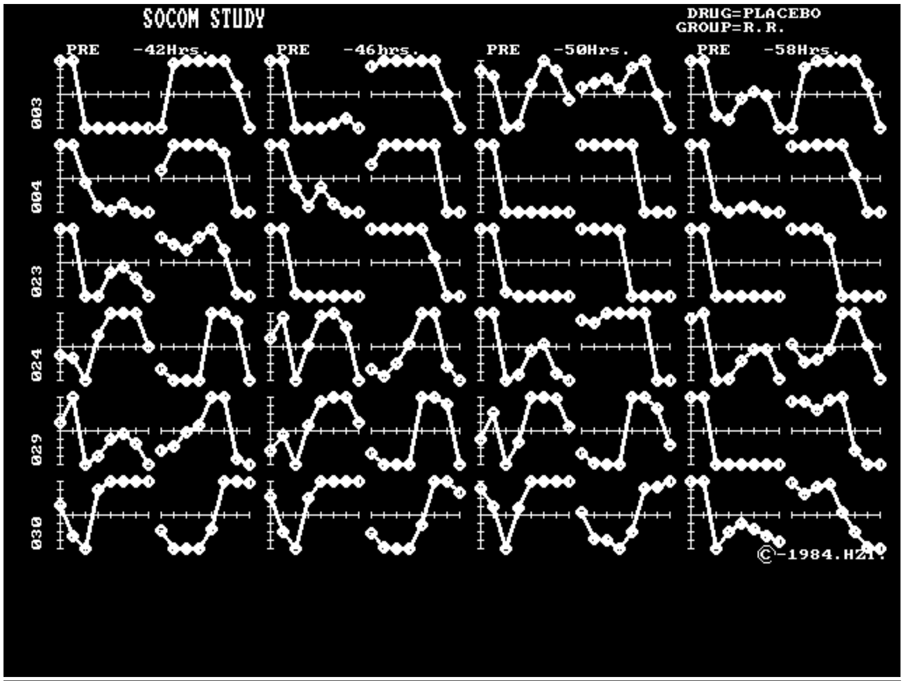


Figure B-14. Individual t-profile for the placebo group (resting recording). Sessions 42, 46, 50, and 58 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.

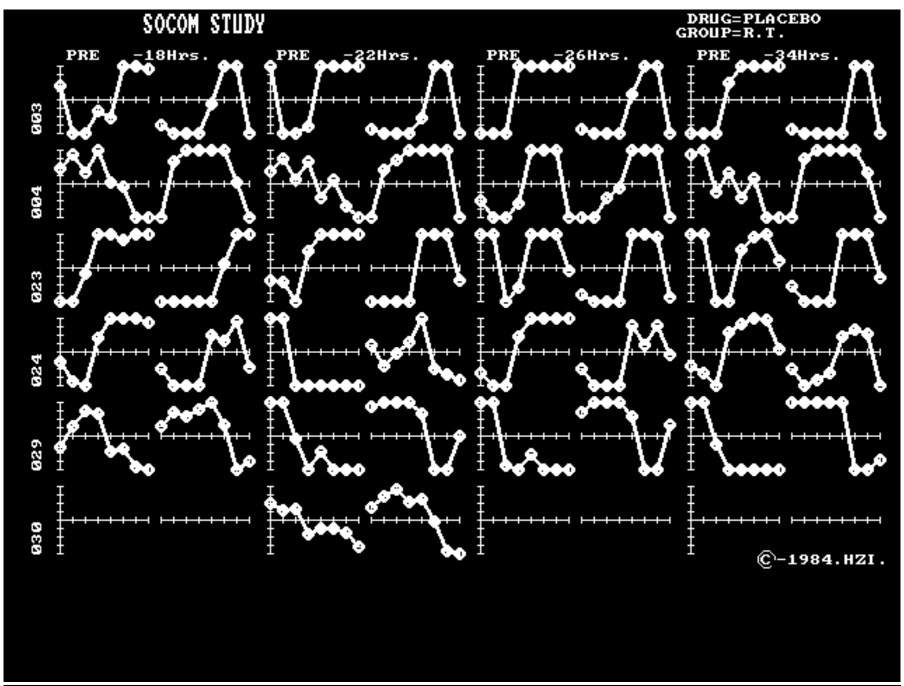
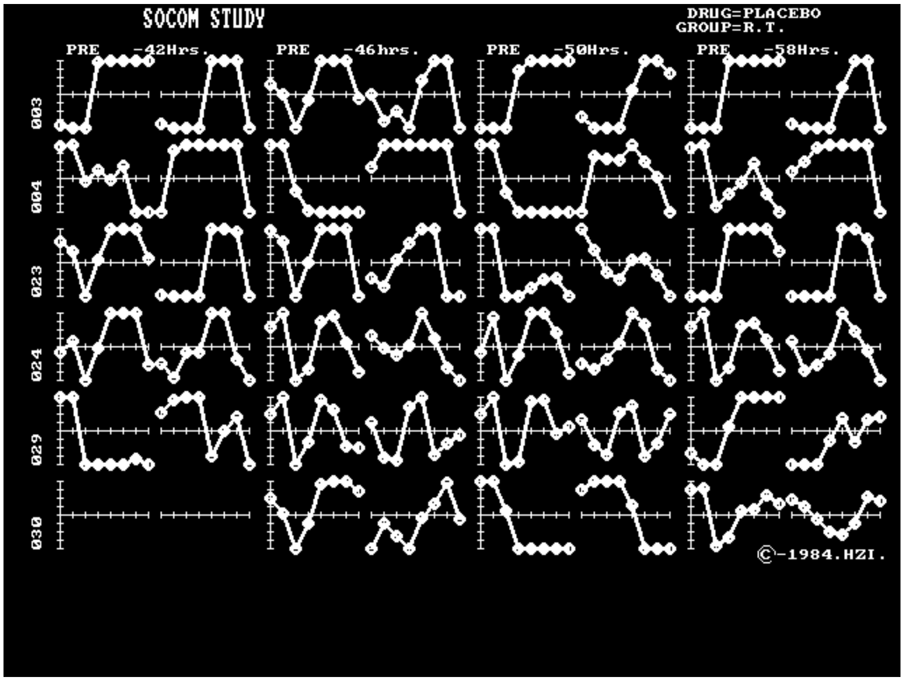


Figure B-15. Individual t-profile for the placebo group (reaction time). Sessions 18, 22, 26, and 34 hr minus pre. Rows represent subjects and columns represent sessions. The graph on the left is primary wave, and the graph on the right is first derivative.


SOCOM STUDY
DRUG=PLACEBO
GROUP=R.T.
PRE -42Hrs.
PRE -46hrs.
PRE -50Hrs.
PRE -58Hrs.
003
004
023
024
029
030
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Appendix C.

Similarity correlation coefficients tables.

Similarity coefficient correlations of selected data base psychotropic drugs vs. caffeine QEEG period analysis – 1HR correlations

DATABASE	CNS DEPRESSANTS SEDATIVES-NEUROLEPTICS		ANXIETY RELIEVERS HYPNOTICS-ANXIOLYTICS		MOOD ELEVATORS THYMOLEPTICS-ANTIDEPRESSANTS		VIGILANCE ENHANCERS ENERGIZERS-PSYCHOSTIMULANTS	
	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.
1	-0.36	-0.33	0.10	0.19	-0.24	0.34	-0.34	-0.62
CAFFEINE	-0.34		0.14		0.05		-0.48	
	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.
1	-0.45	-0.40	0.20	0.01	-0.19	0.09	-0.58	-0.36
CAFFEINE	-0.42		0.11		-0.05		-0.47	
	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.
1	-0.34	0.49	0.13	-0.33	-0.28	0.31	-0.38	-0.14
CAFFEINE	0.07		-0.10		0.02		-0.26	
	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.
1	-0.39	-0.50	0.22	0.24	-0.06	0.15	-0.59	-0.43
CAFFEINE	-0.44		0.23		0.04		-0.51	
	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.
1	-0.51	-0.51	0.39	0.30	-0.25	0.09	-0.39	-0.39
CAFFEINE	-0.51		0.34		-0.08		-0.39	
	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.
1	-0.33	-0.11	0.23	0.31	0.01	0.36	-0.56	-0.45
CAFFEINE	-0.22		0.27		0.19		-0.50	
	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.
1	-0.17	-0.05	0.22	0.26	0.08	0.23	-0.42	-0.33
CAFFEINE	-0.11		0.24		0.16		-0.37	
	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.
1	-0.33	0.08	0.18	0.00	-0.14	0.48	-0.46	-0.51
CAFFEINE	-0.13		0.09		0.17		-0.49	

Similarity coefficient correlations of selected data base psychotropic drugs vs. caffeine QEEG period analysis – 3HR correlations

DATABASE	CNS DEPRESSANTS SEDATIVES-NEUROLEPTICS		ANXIETY RELIEVERS HYPNOTICS-ANXIOLYTICS		MOOD ELEVATORS THYMOLEPTICS-ANTIDEPRESSANTS		VIGILANCE ENHANCERS ENERGIZERS-PSYCHOSTIMULANTS	
	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.
1 CAFFEINE	-0.38	-0.26	0.14	0.18	0.24	0.46	-0.36	-0.53
	-0.32		0.16		0.35		-0.45	
	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.
1 CAFFEINE	-0.28	-0.38	0.28	0.02	0.45	0.23	-0.60	-0.20
	-0.33		0.15		0.34		-0.40	
	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.
1 CAFFEINE	-0.34	0.64	0.19	-0.37	0.26	0.22	-0.41	-0.22
	0.15		-0.09		0.24		-0.31	
	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.
1 CAFFEINE	-0.18	-0.45	0.29	0.24	0.51	0.29	-0.61	-0.26
	-0.31		0.26		0.40		-0.43	
	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.
1 CAFFEINE	-0.37	-0.53	0.44	0.31	0.30	0.25	-0.39	-0.21
	-0.45		0.37		0.27		-0.30	
	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.
1 CAFFEINE	-0.11	-0.08	0.30	0.27	0.51	0.45	-0.57	-0.36
	-0.10		0.28		0.48		-0.47	
	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.
1 CAFFEINE	-0.03	-0.11	0.25	0.23	0.42	0.32	-0.46	-0.22
	-0.07		0.24		0.37		-0.34	
	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.
1 CAFFEINE	-0.20	0.16	0.24	-0.00	0.39	0.56	-0.51	-0.32
	-0.02		0.12		0.48		-0.41	

Similarity coefficient correlations of selected data base psychotropic drugs vs. dextroamphetamine QEEG period analysis – 1HR correlations

DATABASE	CNS DEPRESSANTS SEDATIVES-NEUROLEPTICS		ANXIETY RELIEVERS HYPNOTICS-ANXIOLYTICS		MOOD ELEVATORS THYMOLEPTICS-ANTIDEPRESSANTS		VIGILANCE ENHANCERS ENERGIZERS-PSYCHOSTIMULANTS	
	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.
1	-0.55	-0.33	0.39	0.25	-0.34	0.22	-0.40	-0.47
DEXTROAM	-0.44		0.32		-0.06		-0.44	
	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.
1	-0.52	-0.28	0.34	0.38	-0.36	0.22	-0.31	-0.43
DEXTROAM	-0.40		0.36		-0.07		-0.37	
	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.
1	-0.48	0.04	0.32	0.34	-0.29	0.50	-0.35	-0.59
DEXTROAM	-0.22		0.33		0.11		-0.47	
	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.
1	-0.39	-0.01	0.39	0.43	0.04	0.59	-0.57	-0.68
DEXTROAM	-0.20		0.41		0.31		-0.63	
	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.
1	-0.38	0.01	0.32	0.34	0.05	0.59	-0.62	-0.68
DEXTROAM	-0.18		0.33		0.32		-0.65	
	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.
1	-0.29	-0.09	0.34	0.13	0.21	0.44	-0.68	-0.57
DEXTROAM	-0.19		0.24		0.32		-0.63	
	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.
1	-0.29	-0.08	0.29	0.27	0.15	0.49	-0.57	-0.60
DEXTROAM	-0.19		0.28		0.32		-0.59	
	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.
1	-0.33	0.03	0.30	0.21	0.16	0.63	-0.60	-0.70
DEXTROAM	-0.15		0.25		0.40		-0.65	

Similarity coefficient correlations of selected data base psychotropic drugs vs. dextroamphetamine QEEG period analysis – 3HR correlations

DATABASE	CNS DEPRESSANTS SEDATIVES-NEUROLEPTICS		ANXIETY RELIEVERS HYPNOTICS-ANXIOLYTICS		MOOD ELEVATORS THYMOLEPTICS-ANTIDEPRESSANTS		VIGILANCE ENHANCERS ENERGIZERS-PSYCHOSTIMULANTS	
	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.
1	-0.47	-0.38	0.44	0.26	0.26	0.38	-0.40	-0.31
DEXTROAM	-0.43		0.35		0.32		-0.36	
	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.
1	-0.51	-0.36	0.38	0.38	0.17	0.36	-0.31	-0.34
DEXTROAM	-0.44		0.38		0.27		-0.32	
	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.
1	-0.45	-0.02	0.36	0.33	0.22	0.61	-0.35	-0.51
DEXTROAM	-0.23		0.34		0.41		-0.43	
	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.
1	-0.15	-0.01	0.44	0.41	0.50	0.69	-0.59	-0.62
DEXTROAM	-0.08		0.42		0.60		-0.60	
	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.
1	-0.14	0.02	0.38	0.33	0.57	0.69	-0.64	-0.57
DEXTROAM	-0.06		0.35		0.63		-0.61	
	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.
1	0.02	-0.06	0.40	0.12	0.66	0.57	-0.72	-0.47
DEXTROAM	-0.02		0.26		0.62		-0.60	
	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.
1	-0.06	-0.07	0.33	0.26	0.55	0.62	-0.60	-0.49
DEXTROAM	-0.06		0.30		0.58		-0.55	
	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.
1	-0.05	0.10	0.34	0.20	0.57	0.74	-0.64	-0.61
DEXTROAM	0.03		0.27		0.65		-0.62	

Similarity coefficient correlations of selected data base psychotropic drugs vs. modafinil QEEG period analysis – 1HR correlations

DATABASE	CNS DEPRESSANTS SEDATIVES-NEUROLEPTICS		ANXIETY RELIEVERS HYPNOTICS-ANXIOLYTICS		MOOD ELEVATORS THYMOLEPTICS-ANTIDEPRESSANTS		VIGILANCE ENHANCERS ENERGIZERS-PSYCHOSTIMULANTS	
	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.
1	-0.25	-0.34	0.04	-0.13	-0.51	-0.30	0.22	0.12
MODAFINI	-0.29		-0.05		-0.40		0.17	
	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.
1	-0.27	-0.02	0.46	0.23	0.14	0.14	-0.40	-0.22
MODAFINI	-0.14		0.35		0.14		-0.31	
	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.
1	-0.63	-0.25	0.43	0.26	-0.31	0.36	-0.36	-0.60
MODAFINI	-0.44		0.35		0.02		-0.48	
	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.
1	-0.23	0.33	0.43	0.18	0.41	0.41	-0.61	-0.26
MODAFINI	0.05		0.30		0.41		-0.43	
	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.
1	-0.29	-0.20	0.33	0.44	0.33	0.47	-0.73	-0.60
MODAFINI	-0.24		0.39		0.40		-0.67	
	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.
1	-0.44	-0.14	0.32	0.41	-0.10	0.53	-0.52	-0.62
MODAFINI	-0.29		0.36		0.22		-0.57	
	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.
1	-0.42	-0.15	0.43	0.40	0.11	0.59	-0.63	-0.67
MODAFINI	-0.28		0.41		0.35		-0.65	
	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.
1	-0.32	0.10	0.39	0.39	0.14	0.70	-0.63	-0.69
MODAFINI	-0.11		0.39		0.42		-0.66	

Similarity coefficient correlations of selected data base psychotropic drugs vs. modafinil QEEG period analysis – 3HR correlations

DATABASE	CNS DEPRESSANTS SEDATIVES-NEUROLEPTICS		ANXIETY RELIEVERS HYPNOTICS-ANXIOLYTICS		MOOD ELEVATORS THYMOLEPTICS-ANTIDEPRESSANTS		VIGILANCE ENHANCERS ENERGIZERS-PSYCHOSTIMULANTS	
	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.
1 MODAFINI	-0.45	-0.37	0.04	-0.12	-0.30	-0.22	0.22	0.14
	-0.41		-0.04		-0.26		0.18	
	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.
1 MODAFINI	0.05	-0.04	0.48	0.19	0.38	0.18	-0.37	-0.31
	0.00		0.33		0.28		-0.34	
	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.
1 MODAFINI	-0.45	-0.25	0.48	0.26	0.21	0.49	-0.33	-0.43
	-0.35		0.37		0.35		-0.38	
	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.
1 MODAFINI	0.22	0.46	0.46	0.15	0.58	0.32	-0.59	-0.42
	0.34		0.30		0.45		-0.50	
	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.
1 MODAFINI	0.12	-0.17	0.39	0.43	0.69	0.58	-0.75	-0.55
	-0.02		0.41		0.63		-0.65	
	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.
1 MODAFINI	-0.24	-0.06	0.38	0.39	0.43	0.63	-0.53	-0.58
	-0.15		0.38		0.53		-0.56	
	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.
1 MODAFINI	-0.05	-0.03	0.48	0.39	0.57	0.67	-0.63	-0.62
	-0.04		0.43		0.62		-0.63	
	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.
1 MODAFINI	-0.02	0.22	0.43	0.35	0.57	0.74	-0.63	-0.70
	0.10		0.39		0.66		-0.67	

Similarity coefficient correlations of selected data base psychotropic drugs vs. placebo QEEG period analysis – 1HR correlations

DATABASE	CNS DEPRESSANTS SEDATIVES-NEUROLEPTICS		ANXIETY RELIEVERS HYPNOTICS-ANXIOLYTICS		MOOD ELEVATORS THYMOLEPTICS-ANTIDEPRESSANTS		VIGILANCE ENHANCERS ENERGIZERS-PSYCHOSTIMULANTS	
	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.
1	-0.26	-0.26	0.47	0.39	0.11	0.09	-0.20	-0.26
PLACEBO	-0.26		0.43		0.10		-0.23	
	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.
1	0.29	0.42	0.05	0.35	0.68	0.44	-0.34	-0.27
PLACEBO	0.35		0.20		0.56		-0.30	
	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.
1	0.28	-0.06	0.21	0.55	0.61	0.40	-0.18	-0.44
PLACEBO	0.11		0.38		0.51		-0.31	
	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.
1	0.38	0.12	0.07	0.55	0.74	0.47	-0.15	-0.45
PLACEBO	0.25		0.31		0.61		-0.30	
	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.
1	0.02	0.03	0.26	0.48	0.55	0.40	-0.32	-0.41
PLACEBO	0.03		0.37		0.47		-0.36	
	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.
1	0.14	0.41	0.22	0.49	0.55	0.59	-0.22	-0.42
PLACEBO	0.27		0.35		0.57		-0.32	
	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.
1	0.44	0.57	0.19	0.26	0.78	0.39	-0.17	-0.16
PLACEBO	0.50		0.23		0.59 *		-0.17	
	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.
1	0.57	-0.06	0.02	0.47	0.82	0.26	-0.11	-0.31
PLACEBO	0.25		0.24		0.54 *		-0.21	

Similarity coefficient correlations of selected data base psychotropic drugs vs. placebo QEEG period analysis – 3HR correlations

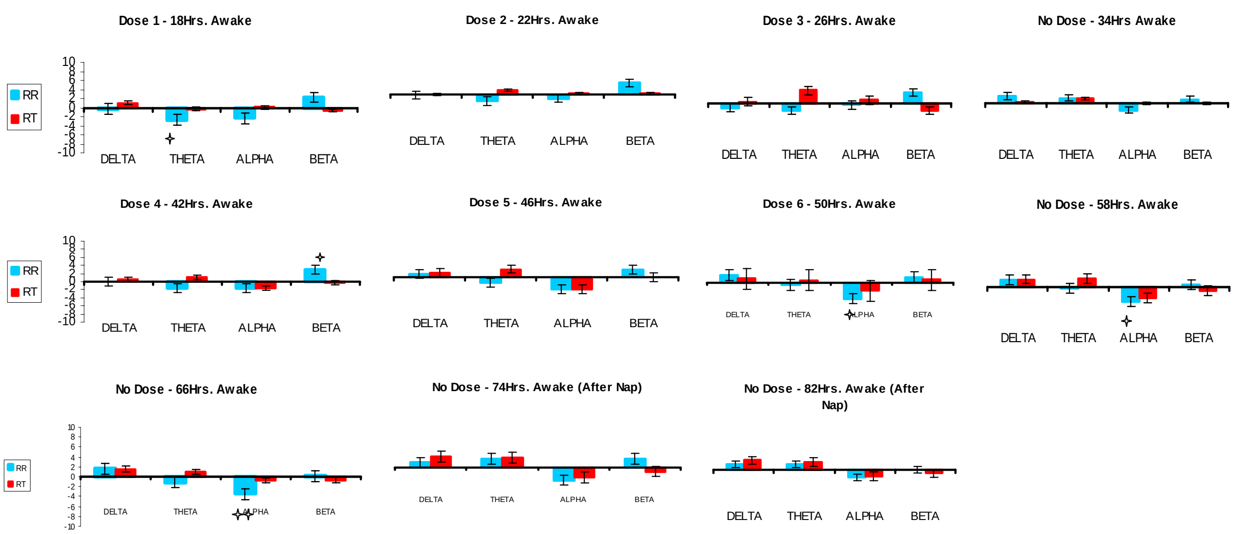
DATABASE	CNS DEPRESSANTS SEDATIVES-NEUROLEPTICS		ANXIETY RELIEVERS HYPNOTICS-ANXIOLYTICS		MOOD ELEVATORS THYMOLEPTICS-ANTIDEPRESSANTS		VIGILANCE ENHANCERS ENERGIZERS-PSYCHOSTIMULANTS	
	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.	18Hrs. R.R.	18Hrs. R.T.
1 PLACEBO	0.04	-0.31	0.48	0.36	0.23	0.16	-0.16	-0.25
	-0.13		0.42		0.19		-0.20	
	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.	22Hrs. R.R.	22Hrs. R.T.
1 PLACEBO	0.65	0.43	0.05	0.29	0.51	0.38	-0.36	-0.37
	0.54		0.17		0.44		-0.37	
	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.	26Hrs. R.R.	26Hrs. R.T.
1 PLACEBO	0.56	-0.09	0.17	0.55	0.32	0.46	-0.20	-0.41
	0.23		0.36		0.39		-0.30	
	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.	34Hrs. R.R.	34Hrs. R.T.
1 PLACEBO	0.66	0.11	0.03	0.52	0.32	0.46	-0.16	-0.46
	0.38		0.28		0.39		-0.31	
	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.	42Hrs. R.R.	42Hrs. R.T.
1 PLACEBO	0.42	0.03	0.25	0.45	0.43	0.41	-0.32	-0.40
	0.22		0.35		0.42		-0.36	
	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.	46hrs. R.R.	46hrs. R.T.
1 PLACEBO	0.46	0.43	0.19	0.44	0.33	0.53	-0.21	-0.52
	0.44		0.31		0.43		-0.37	
	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.	50Hrs. R.R.	50Hrs. R.T.
1 PLACEBO	0.67	0.53	0.13	0.22	0.35	0.31	-0.17	-0.28
	0.60		0.18		0.33		-0.23	
	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.	58Hrs. R.R.	58Hrs. R.T.
1 PLACEBO	0.80	-0.12	-0.03	0.45	0.31	0.32	-0.11	-0.28
	0.34		0.21		0.31		-0.20	

Appendix D.

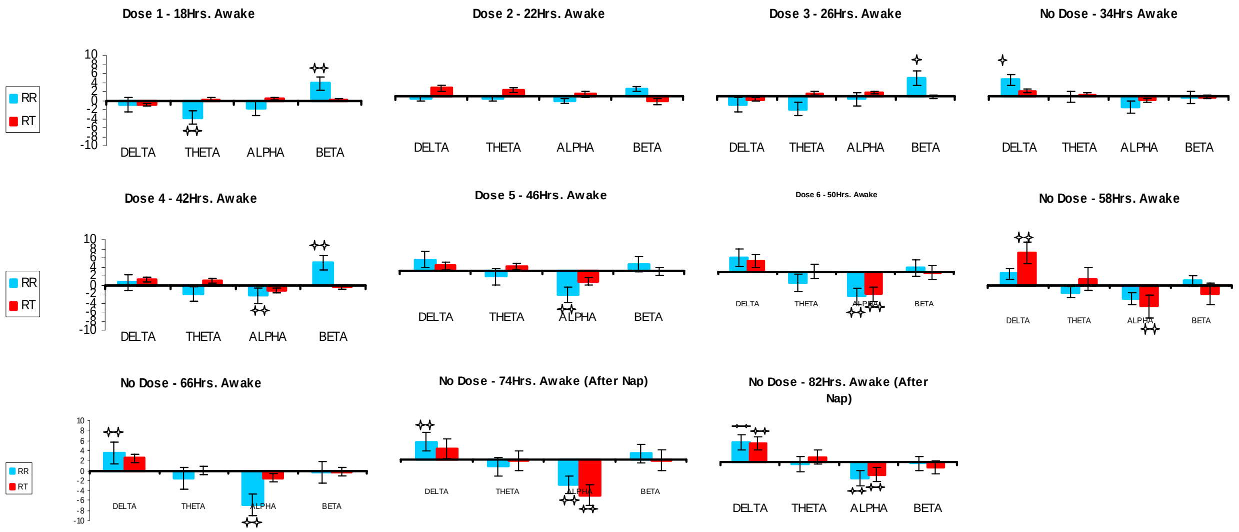
Drug-induced changes graphed for O2, CZ, and FZ.

Caffeine at O2

Caffeine at CZ

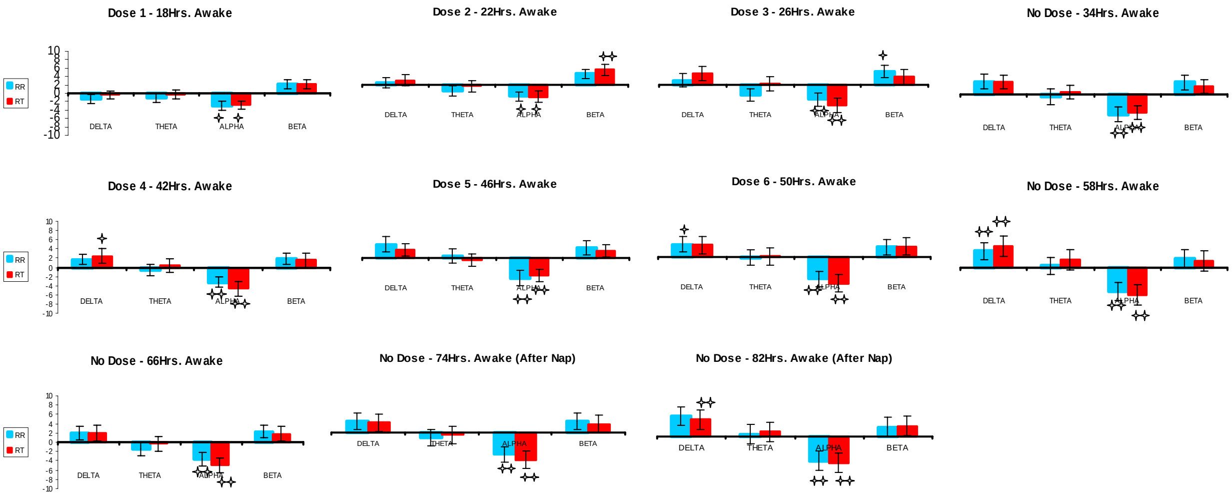


Caffeine at FZ

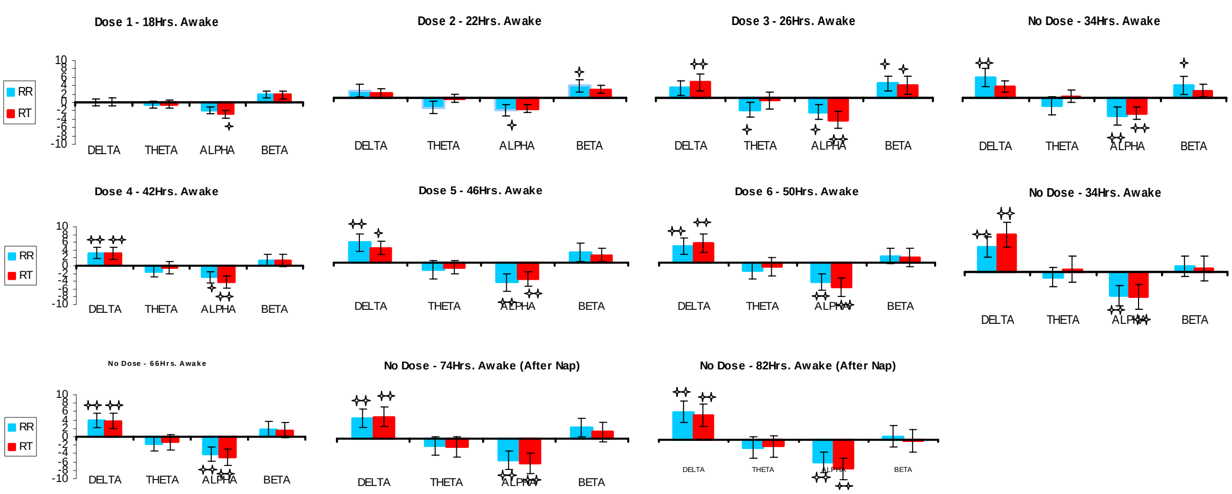


Drug and sleep-deprivation induced changes from baseline to each subsequent time period based on t-values shown from left-to-right, top-to-bottom. Time periods are with 4 frequency bands subdivided by Resting Recording and Reaction Time. (+ = $p < .05$ and ++ = $p < .01$).

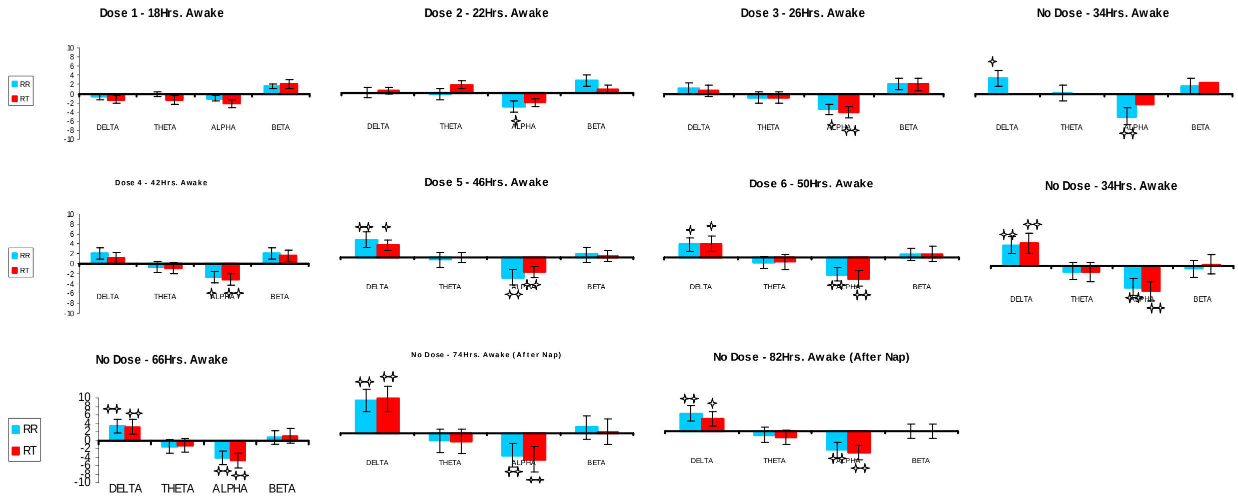
Dextramphetamine at O2



Dextroamphetamine at CZ

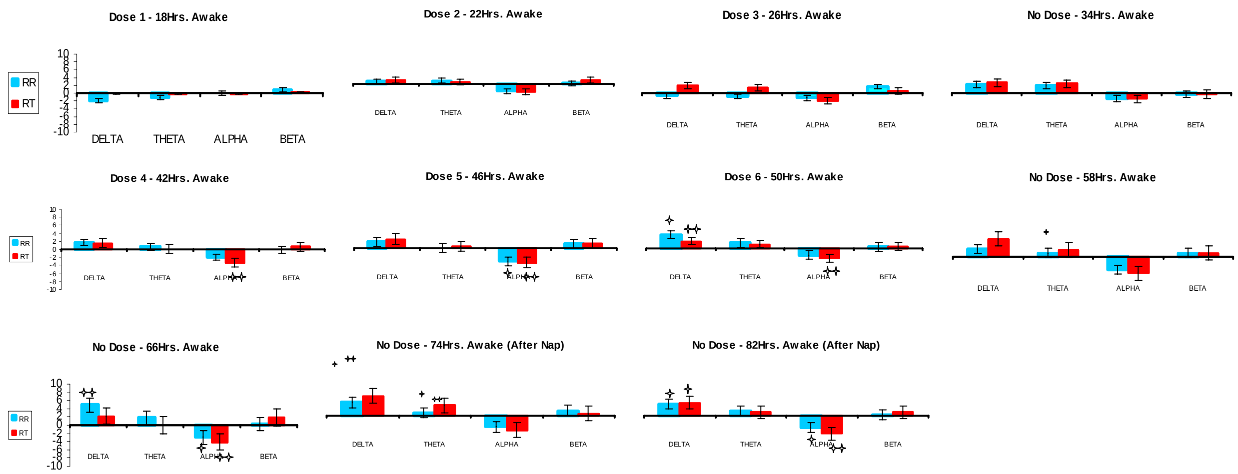


Dextroamphetmine at FZ

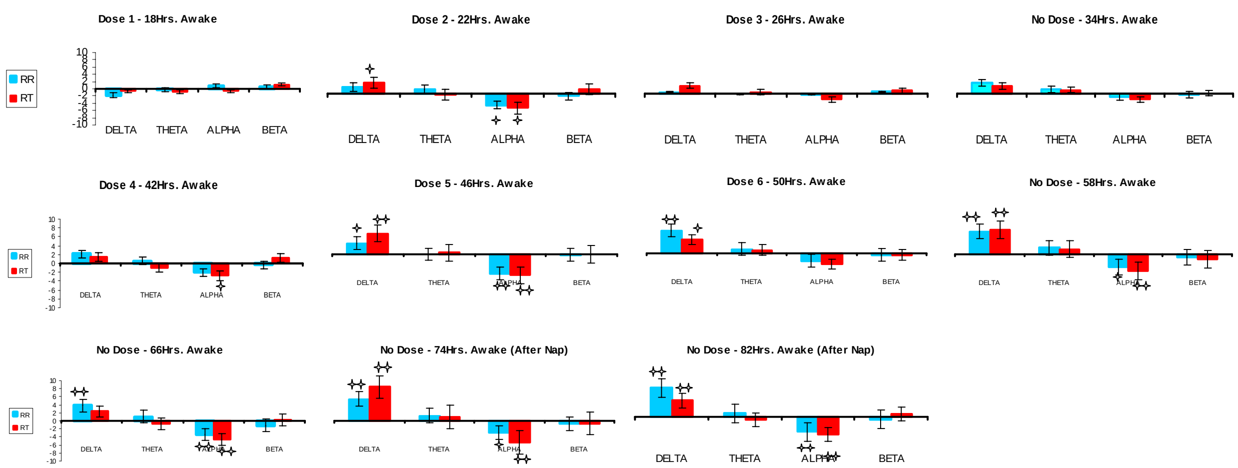


Drug and sleep-deprivation induced changes from baseline to each subsequent time period based on t-values shown from left-to-right, top-to-bottom. Time periods are with 4 frequency bands subdivided by Resting Recording and Reaction Time. (+ = $p < .05$ and ++ = $p < .01$).

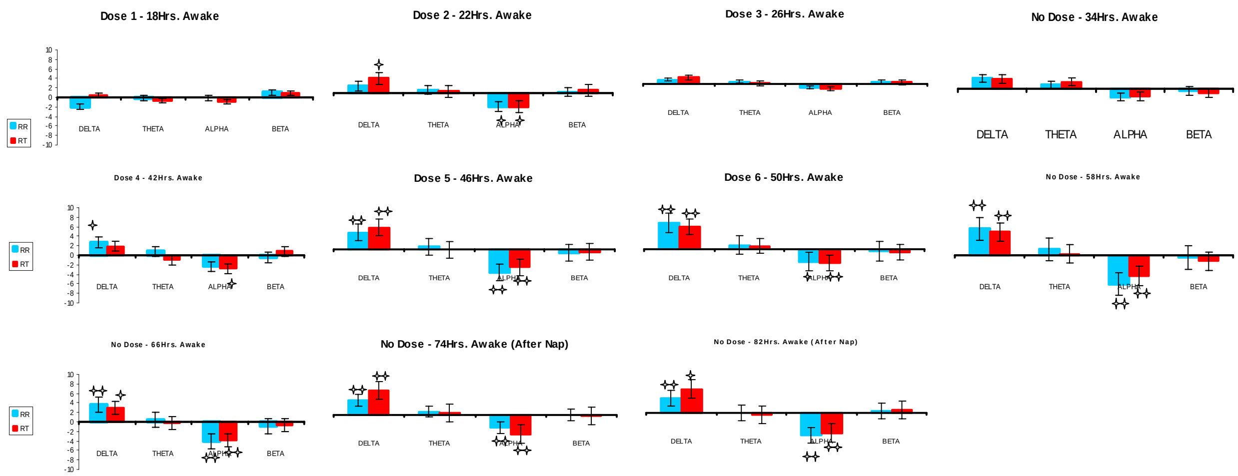
Modafinil at O2



Modafinil at CZ

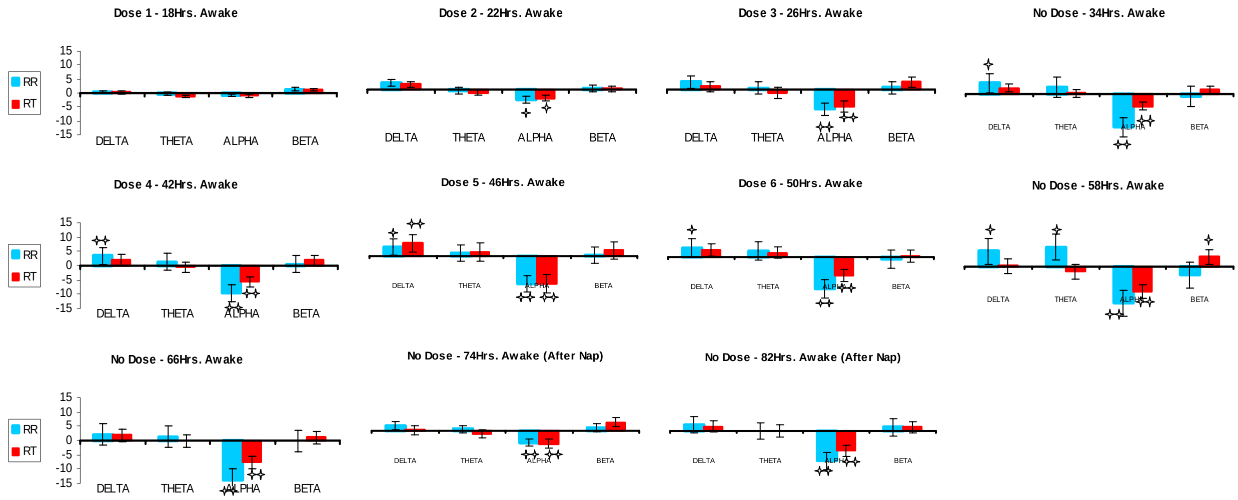


Modafinil at FZ

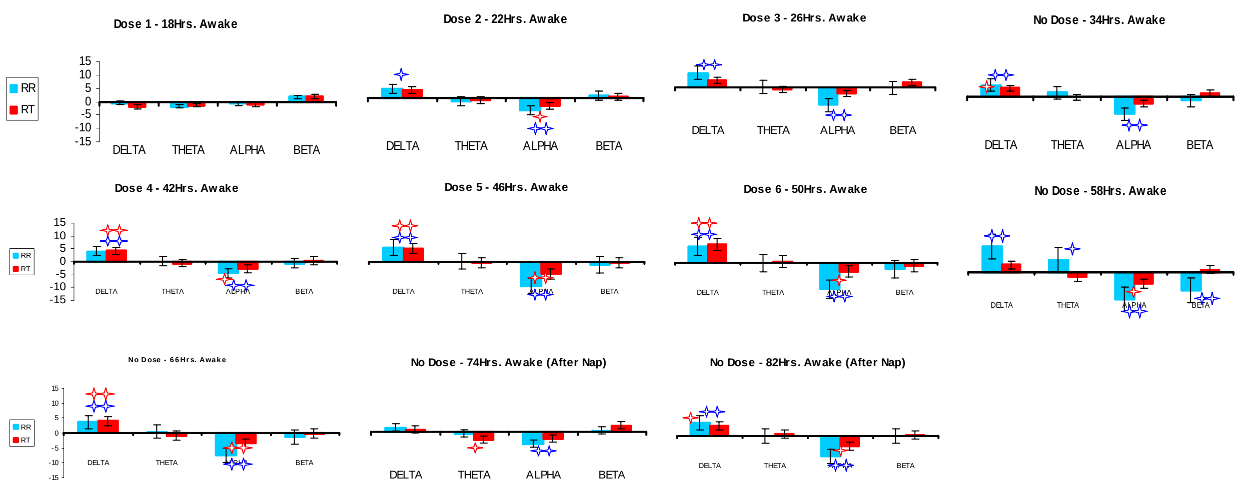


Drug and sleep-deprivation induced changes from baseline to each subsequent time period based on t-values shown from left-to-right, top-to-bottom. Time periods are with 4 frequency bands subdivided by Resting Recording and Reaction Time. (+ = $p < .05$ and ++ = $p < .01$).

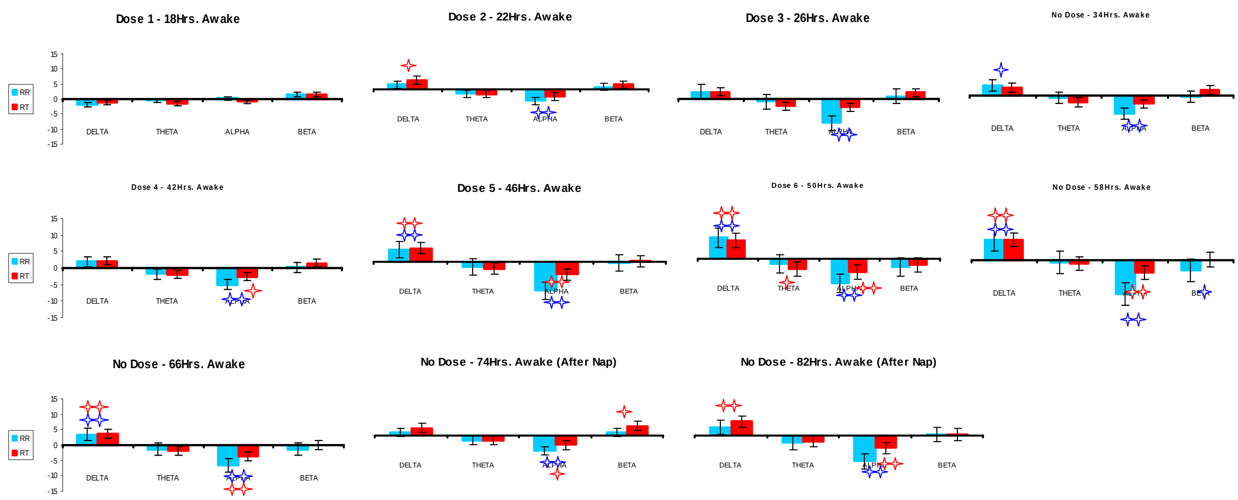
Placebo at O2



Placebo at CZ



Placebo at FZ



Drug and sleep-deprivation induced changes from baseline to each subsequent time period based on t-values shown from left-to-right, top-to-bottom. Time periods are with 4 frequency bands subdivided by Resting Recording and Reaction Time. (+ = $p < .05$ and ++ = $p < .01$).

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